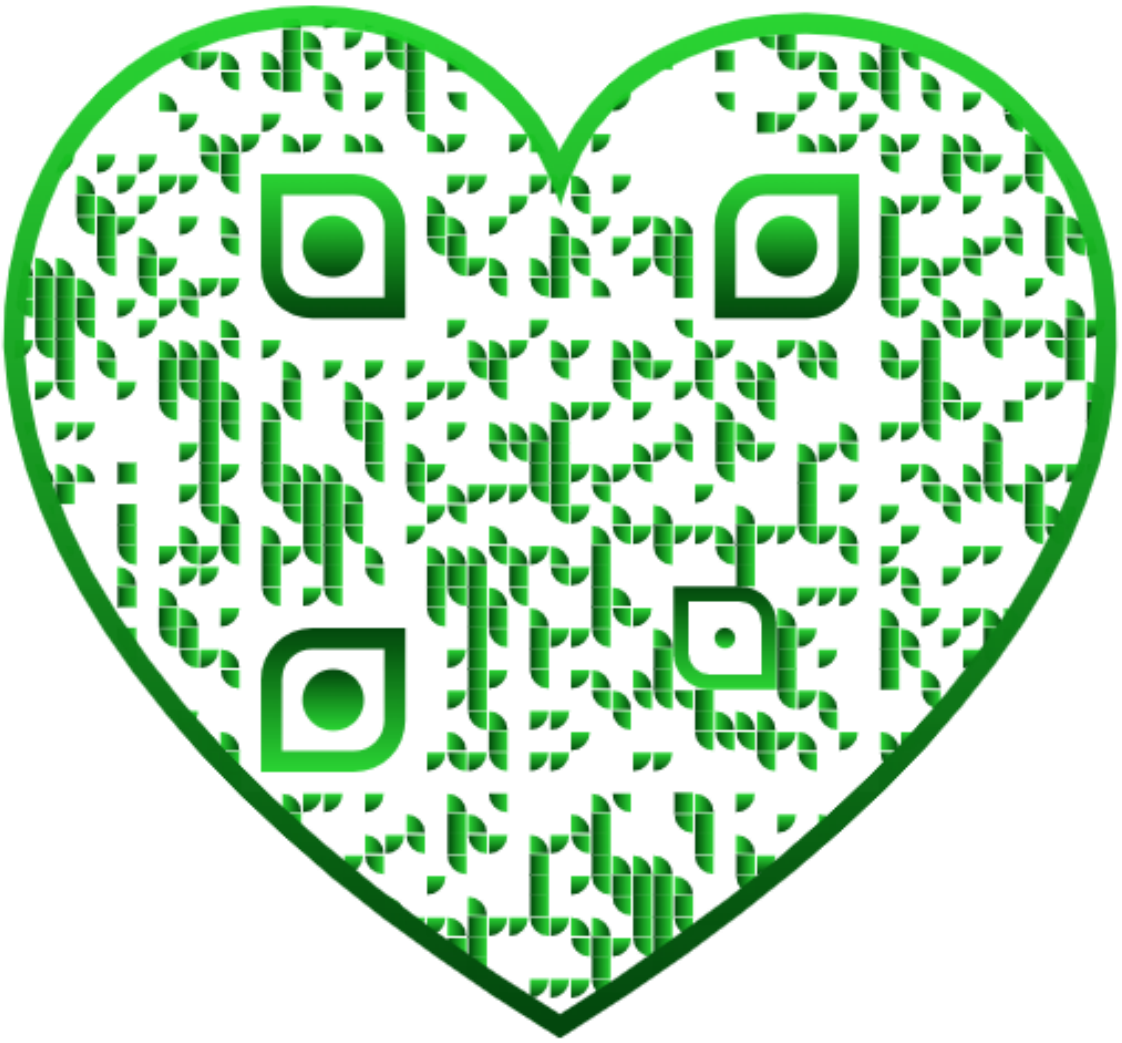
WHO consolidated guidelines on tuberculosis

Module 4: Treatment

Drug-resistant tuberculosis treatment

2022 update

World Health Organization



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Contents

Acknowledgements v

Abbreviations and acronyms ix

Definitions xi

Executive summary xiii

Introduction 1

Recommendations 6

Section 1. The 6-month bedaquiline, pretomanid, linezolid and moxifloxacin (BPaLM) regimen for MDR/RR-TB (NEW) 6

Section 2. The 9-month all-oral regimen for MDR/RR-TB (NEW) 33

Section 3. Longer regimens for MDR/RR-TB 47

Section 4. Regimen for rifampicin-susceptible, isoniazid-resistant TB (Hr-TB) 69

Section 5. Monitoring patient response to MDR/RR-TB treatment using culture 77

Section 6. Starting antiretroviral therapy in patients on MDR/RR-TB regimens 81

Section 7. Surgery for patients on MDR/RR-TB treatment 83

Research gaps 85

References 89

Annex 1. Supplementary table 98

Annex 2. Trial population in ZeNix and TB-PRACTECAL trials 108

Web Annexes

Web Annex 1. Methods and expert panels

Web Annex 2. Declarations of interest

Web Annex 3. GRADE evidence summary tables

Web Annex 4. GRADE evidence-to-decision tables

Web Annex 5. Statistical analysis plan

Web Annex 6. Slide set on data synthesis presented at the GDG meeting 2022

https://apps.who.int/iris/bitstream/handle/10665/365284/9789240063983-eng.pdf

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Abbreviations and acronyms

aDSM	active TB drug-safety monitoring and management
AFB	acid-fast bacilli
AIDS	acquired immunodeficiency syndrome
aIPD	adult individual patient data
aOR	adjusted odds ratio
aRR	adjusted risk ratio
ART	antiretroviral therapy
BMI	body mass index
BPaL	bedaquiline, pretomanid and linezolid
BPaLC	bedaquiline, pretomanid, linezolid and clofazimine
BPaLM	bedaquiline, pretomanid, linezolid and moxifloxacin
CI	confidence interval
CL	confidence limits
CNS	central nervous system
DELIBERATE	DELamanId Bedaquiline for ResistAnt TubErculosis (trial)
DR-TB	drug-resistant tuberculosis
DST	drug susceptibility testing
ECG	electrocardiogram
EDRWeb	Electronic Drug-Resistant Tuberculosis Register (South Africa)
FDC	fixed-dose combination (medicines)
GDF	Global Drug Facility
GDG	Guideline Development Group
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HIV	human immunodeficiency virus
HR	isoniazid–rifampicin
HREZ	isoniazid–rifampicin–ethambutol–pyrazinamide
(H)REZ	(isoniazid optional)–rifampicin–ethambutol–pyrazinamide
Hr-TB	rifampicin-susceptible, isoniazid-resistant tuberculosis
IPD	individual patient data (or dataset)
IQR	interquartile range
LPA	line probe assay
M. tuberculosis	*Mycobacterium tuberculosis*
MDR-TB	multidrug-resistant tuberculosis
MDR/RR-TB	multidrug- or rifampicin-resistant tuberculosis
MIC	minimum inhibitory concentration

MSF	Médecins Sans Frontières
NExT	Newer and Emerging Treatment for MDR/RR-TB (trial)
NTP	national TB programme
PICO	population, intervention, comparator and outcomes
PLHIV	people living with HIV
pre-XDR-TB	pre-extensively drug-resistant tuberculosis
QTcF	corrected QT interval by Fredericia
RCT	randomized controlled trial
RD	risk difference
REZ	rifampicin–ethambutol–pyrazinamide
RR	risk ratio
RR-TB	rifampicin-resistant tuberculosis
SAT	self-administered therapy (also meaning unsupervised treatment)
SRL	TB Supranational Reference Laboratory
STREAM	Standard Treatment Regimen of Anti-tuberculosis Drugs for Patients with MDR-TB (trial)
TB	tuberculosis
US CDC	United States Centers for Disease Control and Prevention
USA	United States of America
WHO	World Health Organization
WHO/GTB	Global Tuberculosis Programme of the World Health Organization
XDR-TB	extensively drug-resistant tuberculosis

TB medicines

B or Bdq	bedaquiline
C or Cfz	clofazimine
Cs	cycloserine
Dlm	delamanid
E	ethambutol
Eto	ethionamide
FQ	fluoroquinolones
H	isoniazid
Hh	isoniazid high dose
Ipm-Cln	imipenem–cilastatin
L or Lzd	linezolid
Lfx	levofloxacin
M or Mfx	moxifloxacin
Mpm	meropenem
P or Rpt	rifapentine
Pa	pretomanid
PAS	*P*-aminosalicylic acid
Pto	prothionamide
R	rifampicin
Z	pyrazinamide

Definitions

Bacteriologically confirmed: when a biological specimen is positive by smear microscopy, culture or a rapid diagnostic test for tuberculosis (TB) recommended by the World Health Organization (WHO).

Clinically diagnosed: when a person who does not fulfil the criteria for bacteriological confirmation has been diagnosed with TB disease by a medical practitioner who has decided to give the person a full course of TB treatment.

Drug-resistant TB (DR-TB): TB disease caused by a strain of *Mycobacterium tuberculosis* complex that is resistant to any TB medicines.

Drug susceptibility testing (DST): in vitro testing using either molecular or genotypic techniques to detect resistance-conferring mutations, or phenotypic methods to determine susceptibility to a medicine.

Extensive (or advanced) pulmonary TB disease: presence of bilateral cavitary disease or extensive parenchymal damage on chest radiography. In children aged below 15 years, advanced disease is usually defined by the presence of cavities or bilateral disease on chest radiography.

Extensively drug-resistant TB (XDR-TB): TB disease caused by a strain of *M. tuberculosis* complex that is resistant to rifampicin (and may also be resistant to isoniazid), and that is also resistant to at least one fluoroquinolone (levofloxacin or moxifloxacin) and to at least one other "Group A" drug (bedaquiline or linezolid).

MDR/RR-TB: refers to either multidrug-resistant TB (MDR-TB) or rifampicin-resistant TB (RR-TB).

Multidrug-resistant TB (MDR-TB): TB disease caused by a strain of *M. tuberculosis* complex that is resistant to rifampicin and isoniazid.

New case: a person with TB disease who has never been treated for TB or has only previously ever taken TB drugs for less than 1 month.

Operational research or **implementation research**: "the use of systematic research techniques for programme decision-making to achieve a specific outcome".[1] In the context of this document, these terms are also applied to research that aims to develop the critical evidence base that informs the effective, sustained and embedded adoption of interventions within a health system, to improve health or patient outcomes. Such research deals with the knowledge gap between efficacy, effectiveness and current practice to produce the greatest gains in disease control.[2] Operational research also provides decision-makers with information to enable them to improve the performance of their health programmes.[3]

---

[1] Allotey P, Reidpath DD, Ghalib H, Pagnoni F, Skelly WC (2008) Efficacious, effective, and embedded interventions: implementation research in infectious disease control. BMC Public Health 2008;8(1):1–6. doi: https://doi.org/10.1186/1471-2458-8-343.

[2] Guide to operational research in programmes supported by the Global Fund. Geneva: Global Fund to Fight AIDS, Tuberculosis and Malaria; 2007.

[3] Expanding capacity for operations research in reproductive health: summary report of a consultative meeting, World Health Organization, Geneva, Switzerland, December 10–12, 2001. Geneva: World Health Organization; 2003 (https://apps.who.int/iris/handle/10665/67936).

Pre-extensively drug-resistant TB (pre-XDR-TB): TB disease caused by a strain of *M. tuberculosis* complex that is resistant to rifampicin (and may also be resistant to isoniazid), and that is also resistant to at least one fluoroquinolone (either levofloxacin or moxifloxacin).

Rifampicin-resistant TB (RR-TB): TB disease caused by a strain of *M. tuberculosis* complex that is resistant to rifampicin. These strains may be susceptible or resistant to isoniazid (i.e. multidrug-resistant TB [MDR-TB]), or resistant to other first-line or second-line TB medicines.

Rifampicin-susceptible, isoniazid-resistant TB (Hr-TB): TB disease caused by a strain of *M. tuberculosis* complex that is resistant to isoniazid but susceptible to rifampicin.

Serious adverse event: an adverse event that leads to death or a life-threatening experience, to hospitalization or prolongation of hospitalization, to persistent or significant disability, or to a congenital anomaly. Adverse events that do not immediately result in one of these outcomes but that require an intervention to prevent such an outcome from happening are included. Serious adverse events may require a drastic intervention, such as termination of the drug suspected of having caused the event.

Severe extrapulmonary TB: presence of miliary TB, TB meningitis, osteoarticular or pericardial TB. In children aged below 15 years, extrapulmonary forms of disease other than lymphadenopathy (peripheral nodes or isolated mediastinal mass without compression) are considered severe.

Tuberculosis (TB) disease: A disease in humans caused by the *M. tuberculosis* complex, which comprises eight distinct but closely related organisms – *M. bovis, M. caprae, M. africanum, M. microti, M. pinnipedii, M. mungi, M. orygis* and *M. canetti*. The most common and important agent of human disease is *M. tuberculosis*.

TB case: the occurrence of TB disease in a person.

TB patient: a person who is in care for TB disease.

Executive summary

Tuberculosis (TB) strains that are resistant to TB medicines are more difficult to treat than drug-susceptible ones, and present a major challenge for patients, health care workers and health care services. In addition, the increase of drug-resistant TB (DR-TB) threatens global progress towards the targets set by the End TB Strategy[4] of the World Health Organization (WHO). Thus, there is a critical need for the continual development of evidence-based policy recommendations on the treatment and care of patients with DR-TB, based on the most recent and comprehensive evidence available.

In the past decade, WHO has developed and issued evidence-based policy recommendations for the treatment and care of patients with DR-TB, published in a range of documents (see **Box 1**). WHO has recently started to consolidate guidelines, in response to requests from Member States, to facilitate policy transfer at the country level. The first integrated recommendations for the management and care of multidrug- or rifampicin-resistant TB (MDR/RR-TB) were released in 2019, as the *WHO consolidated guidelines on drug-resistant tuberculosis treatment*.[5] The consolidation of WHO recommendations on TB and DR-TB has now been expanded to better outline the path that a patient will take following exposure to resistant strains of *Mycobacterium tuberculosis*, once infection has progressed to TB disease, and the patient has been identified by the health system and referred for DR-TB treatment.

The guidance provided in this sub-module under TB treatment policy outlines specific WHO recommendations on the overall treatment management, care and monitoring of patients with MDR/RR-TB. It brings forward recommendations developed by various Guideline Development Groups (GDGs) convened by WHO. The GDGs use the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to summarize the evidence, and formulate policy recommendations and accompanying remarks (**Sections 2–7**). This sub-module also incorporates new recommendations that were made in February and March 2022 (**Sections 1–2**), based on new evidence that was available to WHO on the following: the use of the bedaquiline, pretomanid,[6] linezolid and moxifloxacin (BPaLM) regimen for patients with MDR/RR-TB, and the use of 9-month all-oral bedaquiline-containing regimens for patients with MDR/RR-TB. The inclusion of these two new recommendations in the current update of the consolidated guidelines was communicated to the public via a rapid communication in May 2022.[7] This rapid communication was released in advance of updated WHO consolidated guidelines, to inform national TB programmes (NTPs) and other stakeholders of key changes in the treatment of DR-TB and to allow for rapid transition and planning at the country level.

Overall, this sub-module focuses on recommendations for the use of effective treatment regimens for people with DR-TB; specifically, regimens for rifampicin-susceptible, isoniazid-resistant TB (Hr-TB), all-oral shorter regimens for MDR/RR-TB, longer regimens for MDR/RR-TB, monitoring the patient response to MDR/RR-TB treatment, starting antiretroviral therapy (ART) in patients on second-line anti-TB regimens and providing surgery for patients on MDR-TB treatment. Additionally, to inform

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4 The End TB Strategy. Geneva: World Health Organization; 2015 (https://www.who.int/teams/global-tuberculosis-programme/the-end-tb-strategy).

5 WHO consolidated guidelines on drug-resistant tuberculosis treatment (WHO/CDS/TB/2019.7). Geneva: World Health Organization; 2019 (https://apps.who.int/iris/handle/10665/311389).

6 Pretomanid is a new chemical entity and a member of a class of compounds known as nitroimidazo-oxazines, which possess significant anti-TB activity and a unique mechanism of action.

7 Rapid communication: key changes to the treatment of drug-resistant tuberculosis. Geneva: World Health Organization; 2022 (https://www.who.int/publications/i/item/WHO-UCN-TB-2022–2).

the global community of the major gaps and research areas to be addressed and to inform the development of evidence-based recommendations, this document outlines the research priorities that will help to generate knowledge on evidence-based and attainable standards of health.

In this updated document, stakeholders will be able to distinguish between previous recommendations that remain valid, previous recommendations that have been updated, and new recommendations that have been developed based on additional studies, considering the range of known benefits and potential harms, modelling exercises and other data to inform the decision-making process.

The recommendations included herein are a component of the WHO consolidated guidelines on TB and are primarily intended for use by NTPs, public health agencies, and other key constituencies involved in the planning, implementation and monitoring of activities for the programmatic management of DR-TB.

The methods used to develop and formulate the recommendations complied with WHO standards for guideline development, and were based on up-to-date evidence reviews, complemented with additional information on values and preferences, feasibility and acceptability, and cost. The GRADE approach was used to rate the certainty in the estimate of effect (i.e. quality of evidence) as high, moderate, low or very low; it was also used to determine the strength of the recommendations, rating them as strong or conditional.

Current WHO recommendations on the treatment of DR-TB

The recommendations for the treatment of DR-TB that are presented in this document have been derived from earlier WHO guideline documents (**Box 1**), and a WHO guideline development conducted in February–March 2022. These recommendations supersede the *WHO consolidated guidelines on tuberculosis. Module 4: Treatment – drug-resistant tuberculosis treatment*, that were published in 2020.[8]

[8] WHO consolidated guidelines on tuberculosis. Module 4: Treatment – drug-resistant tuberculosis treatment. Geneva: World Health Organization; 2020 (https://www.who.int/publications/i/item/9789240007048).

Box 1. WHO treatment guidelines containing recommendations that are incorporated into the present sub-module on DR-TB treatment

- Guidelines for the programmatic management of drug-resistant tuberculosis: 2011 update. Geneva: World Health Organization; 2011 (WHO/HTM/TB/2011.6).
- The use of bedaquiline in the treatment of multidrug-resistant tuberculosis: interim policy guidance. Geneva: World Health Organization; 2013 (WHO/HTM/TB/2013.6).
- The use of delamanid in the treatment of multidrug-resistant tuberculosis: interim policy guidance. Geneva: World Health Organization; 2014 (WHO/HTM/TB/2014.23).
- The use of delamanid in the treatment of multidrug-resistant tuberculosis in children and adolescents: interim policy guidance. Geneva: World Health Organization; 2016 (WHO/HTM/TB/2016.14).
- WHO treatment guidelines for drug resistant tuberculosis: 2016 update. Geneva: World Health Organization; 2016 (WHO/HTM/TB/2016.4).
- WHO treatment guidelines for isoniazid-resistant tuberculosis. Supplement to the WHO treatment guidelines for drug-resistant tuberculosis. Geneva: World Health Organization; 2018 (WHO/CDS/TB/2018.7).
- WHO treatment guidelines for multidrug- and rifampicin-resistant tuberculosis, 2018 update. Geneva: World Health Organization; 2018 (WHO/CDS/TB/2018.15).
- WHO consolidated guidelines on drug-resistant tuberculosis treatment. Geneva: World Health Organization; 2019 (WHO/CDS/TB/2019.7).
- WHO consolidated guidelines on tuberculosis. Module 4: treatment – drug-resistant tuberculosis treatment. Geneva: World Health Organization; 2020 (ISBN 978–92–4-000704–8).
- WHO consolidated guidelines on tuberculosis. Module 5: management of tuberculosis in children and adolescents. Geneva: World Health Organization; 2022. Licence: CC BY-NC-SA 3.0 IGO.

This module contains recommendations on treatment regimens for MDR/RR-TB and Hr-TB, including all-oral shorter and longer regimens for MDR/RR-TB, monitoring of patients on treatment, the timing of ART in MDR/RR-TB patients living with HIV and the use of surgery for patients receiving MDR-TB treatment. The recommendations are presented in **Table A** below and labelled as either a new recommendation (where based on a review of new evidence) or a reprinted recommendation (where no new evidence was available or searched for the review).

Table A. List of recommendations in the 2022 update, where (a) is a new recommendation based on review of the new evidence and (b) is a reprinted recommendation where no new evidence was available or searched for the review.

1. The 6-month bedaquiline, pretomanid, linezolid and moxifloxacin (BPaLM) regimen for MDR/RR-TB and pre-XDR-TB (a)	
1.1	WHO suggests the use of the 6-month treatment regimen composed of bedaquiline, pretomanid, linezolid (600 mg) and moxifloxacin (BPaLM) rather than 9-month or longer (18-month) regimens in MDR/RR-TB patients. *(Conditional recommendation, very low certainty of evidence)*
2. The 9-month all-oral regimen for MDR/RR-TB (a)	
2.1	WHO suggests the use of the 9-month all-oral regimen rather than longer (18-month) regimens in patients with MDR/RR-TB and in whom resistance to fluoroquinolones has been excluded. *(Conditional recommendation, very low certainty of evidence)*
3. Longer regimens for MDR/RR-TB (b)	
3.1	In multidrug- or rifampicin-resistant tuberculosis (MDR/RR-TB) patients on longer regimens, all three Group A agents and at least one Group B agent should be included to ensure that treatment starts with at least four TB agents likely to be effective, and that at least three agents are included for the rest of the treatment if bedaquiline is stopped. If only one or two Group A agents are used, both Group B agents are to be included. If the regimen cannot be composed with agents from Groups A and B alone, Group C agents are added to complete it. *(Conditional recommendation, very low certainty of evidence)*
3.2	**Kanamycin and capreomycin** are not to be included in the treatment of MDR/RR-TB patients on longer regimens. *(Conditional recommendation, very low certainty of evidence)*
3.3	**Levofloxacin or moxifloxacin** should be included in the treatment of MDR/RR-TB patients on longer regimens. *(Strong recommendation, moderate certainty of evidence)*
3.4	**Bedaquiline** should be included in longer multidrug-resistant TB (MDR-TB) regimens for patients aged 18 years or more. *(Strong recommendation, moderate certainty of evidence)* **Bedaquiline** may also be included in longer MDR-TB regimens for patients aged 6–17 years. *(Conditional recommendation, very low certainty of evidence)* In children with MDR/RR-TB aged below 6 years, an all-oral treatment regimen containing **bedaquiline** may be used. *(Conditional recommendation, very low certainty of evidence)*
3.5	**Linezolid** should be included in the treatment of MDR/RR-TB patients on longer regimens. (*Strong recommendation, moderate certainty of evidence*)

3.6	**Clofazimine and cycloserine or terizidone** may be included in the treatment of MDR/RR-TB patients on longer regimens. *(Conditional recommendation, very low certainty of evidence)*
3.7	**Ethambutol** may be included in the treatment of MDR/RR-TB patients on longer regimens. *(Conditional recommendation, very low certainty of evidence)*
3.8	**Delamanid** may be included in the treatment of MDR/RR-TB patients aged 3 years or more on longer regimens. (*Conditional recommendation, moderate certainty of evidence*) In children with MDR/RR-TB aged below 3 years **delamanid** may be used as part of longer regimens. *(Conditional recommendation, very low certainty of evidence)*
3.9	**Pyrazinamide** may be included in the treatment of MDR/RR-TB patients on longer regimens. *(Conditional recommendation, very low certainty of evidence)*
3.10	**Imipenem–cilastatin or meropenem** may be included in the treatment of MDR/RR-TB patients on longer regimens. *(Conditional recommendation, very low certainty of evidence)*[9]
3.11	**Amikacin** may be included in the treatment of MDR/RR-TB patients aged 18 years or more on longer regimens when susceptibility has been demonstrated and adequate measures to monitor for adverse reactions can be ensured. If amikacin is not available, streptomycin may replace amikacin under the same conditions. (*Conditional recommendation, very low certainty in the estimates of effect*)
3.12	**Ethionamide or prothionamide** may be included in the treatment of MDR/RR-TB patients on longer regimens only if bedaquiline, linezolid, clofazimine or delamanid are not used, or if better options to compose a regimen are not possible. (*Conditional recommendation against use, very low certainty of evidence)*
3.13	***P*-aminosalicylic acid** may be included in the treatment of MDR/RR-TB patients on longer regimens only if bedaquiline, linezolid, clofazimine or delamanid are not used, or if better options to compose a regimen are not possible. (*Conditional recommendation against use, very low certainty of evidence*)
3.14	**Clavulanic acid** should not be included in the treatment of MDR/RR-TB patients on longer regimens. (*Strong recommendation against use, low certainty of evidence*)[9]
3.15	In MDR/RR-TB patients on longer regimens, a **total treatment duration of 18–20 months** is suggested for most patients; the duration may be modified according to the patient's response to therapy. *(Conditional recommendation, very low certainty of evidence)*

[9] Imipenem–cilastatin and meropenem are administered with clavulanic acid, which is available only in formulations combined with amoxicillin. Amoxicillin–clavulanic acid is not counted as an additional effective TB agent, and it should not be used without imipenem–cilastatin or meropenem.

3.16	In MDR/RR-TB patients on longer regimens, a **treatment duration of 15–17 months after culture conversion** is suggested for most patients; the duration may be modified according to the patient's response to therapy. *(Conditional recommendation, very low certainty of evidence)*
3.17	In MDR/RR-TB patients on longer regimens containing amikacin or streptomycin, **an intensive phase of 6–7 months** is suggested for most patients; the duration may be modified according to the patient's response to therapy. *(Conditional recommendation, very low certainty of evidence)*
4. Regimen for rifampicin-susceptible and isoniazid-resistant TB (b)	
4.1	In patients with confirmed rifampicin-susceptible, isoniazid-resistant tuberculosis , treatment with rifampicin, ethambutol, pyrazinamide and levofloxacin is recommended for a duration of 6 months. (*Conditional recommendation, very low certainty in the estimates of effect*)
4.2	In patients with confirmed rifampicin-susceptible, isoniazid-resistant tuberculosis, it is not recommended to add streptomycin or other injectable agents to the treatment regimen. *(Conditional recommendation, very low certainty of evidence)*
5. Monitoring patient response to MDR/RR-TB treatment using culture (b)	
5.1	In multidrug- or rifampicin-resistant tuberculosis (MDR/RR-TB) patients on longer regimens, the performance of sputum culture in addition to sputum smear microscopy is recommended to monitor treatment response. It is desirable for sputum culture to be repeated at monthly intervals. (*Strong recommendation, moderate certainty in the estimates of test accuracy*)
6. Starting antiretroviral therapy in patients on MDR/RR-TB regimens (b)	
6.1	Antiretroviral therapy is recommended for all patients with HIV and drug-resistant tuberculosis requiring second-line antituberculosis drugs, irrespective of CD4 cell count, as early as possible (within the first 8 weeks) following initiation of antituberculosis treatment. (*Strong recommendation, very low certainty of evidence*)
7. Surgery for patients on MDR/RR-TB treatment (b)	
7.1	In patients with rifampicin-resistant tuberculosis (RR-TB) or multidrug-resistant TB (MDR-TB), elective partial lung resection (lobectomy or wedge resection) may be used alongside a recommended MDR-TB regimen. *(Conditional recommendation, very low certainty of evidence)*

BPaLM: bedaquiline, pretomanid, linezolid (600 mg) and moxifloxacin; HIV: human immunodeficiency virus; MDR/RR-TB: multidrug-resistant or rifampicin-resistant TB; TB: tuberculosis; WHO: World Health Organization; XDR-TB: extensively drug-resistant TB.

Introduction

Drug-resistant tuberculosis (DR-TB) continues to be a public health problem, taking a heavy toll on patients, communities and health care systems. Recent global estimates indicate that there were about half a million new cases of multidrug- or rifampicin-resistant TB (MDR/RR-TB) in 2018, with less than 40% of the estimated burden being notified and 32% reported to have started second-line treatment *(1)*. Current treatment regimens for MDR/RR-TB patients are far from satisfactory. Compared with treatments for drug-susceptible forms of TB, these regimens require a longer course of treatment, a higher pill burden and the use of medicines with a higher toxicity profile; in addition, patients may develop significant adverse events and have poorer treatment outcomes. Globally, although treatment success rates have increased, almost 15% of patients with MDR/RR-TB die from the disease *(1)*.

The Global Tuberculosis Programme of the World Health Organization (WHO/GTB) is now combining all current recommendations into one overall set of consolidated guidelines on TB. The guidelines will contain recommendations pertaining to all areas related to the programmatic management of TB (e.g. screening, preventive treatment, diagnostics, patient support, and the treatment of drug-susceptible TB and DR-TB). The consolidated guidelines will contain modules specific to each programmatic area. This current module concerns the treatment of DR-TB; it presents WHO recommendations that have been newly developed and are published here for the first time, and existing recommendations that have been published in other WHO guidelines that applied the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.

Structure of the document

The recommendations part of this document has seven main sections that cover aspects of the treatment of DR-TB. The aspects covered are:

- the 6-month bedaquiline, pretomanid, linezolid and moxifloxacin (BPaLM) regimen for patients with MDR/RR-TB or pre-extensively drug-resistant TB (pre-XDR-TB) (**Section 1**);
- the 9-month all-oral regimens for MDR/RR-TB (**Section 2**);
- the composition and duration of longer regimens for MDR/RR-TB (**Section 3**);
- the treatment of rifampicin-susceptible and isoniazid-resistant TB (Hr-TB) (**Section 4**);
- monitoring of the patient response to MDR/RR-TB treatment (**Section 5**);
- antiretroviral therapy (ART) for people on MDR/RR-TB regimens (**Section 6**);
- the role of surgery for patients on MDR/RR-TB treatment (**Section 7**);

Each section starts with the current WHO recommendations for that aspect, then gives information on the evidence used to inform that recommendation; a summary of the analyses that were carried out based on the evidence; considerations for specific subgroups; and considerations for implementation, and monitoring and evaluation. Research gaps identified for each of the sections are then presented. Web annexes provide more details on the methods, the Guideline Development Groups (GDGs), the analyses, unpublished data and statistical analysis plans. Additional information on the management of MDR/RR-TB is presented in the relevant chapter of the *WHO operational handbook on tuberculosis*, a separate document that is designed to aid implementation efforts *(2, 3)*. The detailed recommendations presented here replace all previous and current WHO guidelines on the treatment of DR-TB.

Background

Effective treatment of TB, including its drug-resistant forms, relies on the use of several medicines administered in combination for an adequate duration. Significant progress has been made in recent years in identifying more efficacious, safer medicines and shorter treatment regimens. Since the 1990s, WHO has regularly evaluated evidence on the use of specific drug compositions and combinations of regimens of different durations *(4–13)*. Historically, patients with certain drug-resistance patterns were often treated for 20 months or longer. In 2016, a standardized shorter treatment regimen (9–12 months) was recommended for patients with MDR/RR-TB strains not resistant to fluoroquinolones or second-line injectable agents, although longer regimens (18–20 months) continued to be an option for patients who were not eligible for the shorter option. Subsequent modifications to these treatment regimens led WHO to assess new evidence, which in turn resulted in revised recommendations, balancing effectiveness and harms of new regimens or modifications of recommended regimens.

Interest in reducing the duration of treatment for MDR/RR-TB has driven several initiatives in recent years to treat patients with shorter regimens under programmatic and trial conditions *(14–19)*. When used in carefully selected patients with MDR/RR-TB who have not been previously exposed or do not have additional resistance to second-line medicines, these regimens can achieve relapse-free cure in about 80% of cases or more, even under programmatic conditions *(14, 18)*. In 2016, on the basis of data from observational studies of the standardized shorter regimens in various countries in Africa and Asia, WHO for the first time recommended a standardized 9–12-month shorter MDR-TB regimen for eligible patients *(11)*. In 2018, following the results of a trial – the Standard Treatment Regimen of Anti-tuberculosis Drugs for Patients with MDR-TB (STREAM) Stage 1 trial – a revised recommendation on the use of a shorter MDR-TB regimen was released, following an evidence assessment and a ranking of benefits and harms attributed to specific drugs; the revision included a recommendation to replace the injectable agent, kanamycin (or capreomycin), with amikacin *(12)*.

Evidence of permanent effects attributed to the toxicity of injectable agents have prompted further advances in the development of new treatments such as shorter injectable-sparing regimens. In particular, South Africa's Department of Health shared with WHO observational data on an all-oral bedaquiline-containing shorter regimen of 9 months duration. That regimen was reviewed and has been recommended by WHO since 2019, with the following combination of medicines: bedaquiline (used for 6 months), in combination with levofloxacin/moxifloxacin, ethionamide, ethambutol, isoniazid (high-dose), pyrazinamide and clofazimine for 4 months (with the possibility of extending to 6 months if the patient remains sputum smear positive at the end of 4 months); followed by 5 months of treatment with levofloxacin/moxifloxacin, clofazimine, ethambutol and pyrazinamide (4–6 Bdq[6]-Lfx[Mfx]-Eto-E-Z-Hh-Cfz / 5 Lfx[Mfx]-Cfz-Z-E).

The pressing need for more effective treatment regimens for patients with extensive drug resistance, including fluoroquinolone resistance and more extensive drug-resistance profiles, has been the driver for several studies and initiatives to test more effective and novel treatment regimens, including newer and repurposed medicines. One of the first studies was the Nix-TB study, conducted by the TB Alliance. The Nix-TB study was a one-arm, Phase 3, open-label observational cohort study that assessed the safety, efficacy, tolerability and pharmacokinetic properties of a 6-month bedaquiline, pretomanid and linezolid (BPaL) treatment regimen, extendable to 9 months for those who missed doses, or remained culture positive or reverted from culture negative to positive between months 4 and 6 of treatment *(20)*. The study was conducted between 2014 and 2019 at three study sites, all in South Africa, with the first patient enrolled in April 2015. The Nix-TB study contributed evidence to WHO that was reviewed by the GDG in November 2019 and gave rise to the previous recommendation for the use of the BPaL regimen in pre-XDR-TB patients, under operational research conditions. Two randomized controlled trials (RCTs) that concluded in 2021 (TB-PRACTECAL and ZeNix) provided new evidence and prompted assessment by WHO to develop new or updated recommendations on MDR/RR-TB treatment.

Scope of the 2022 update and available evidence

This current module on DR-TB treatment provides specific recommendations on the treatment of DR-TB, including use of regimens for rifampicin-susceptible, isoniazid-resistant TB (Hr-TB), all-oral shorter regimens for MDR/RR-TB, longer regimens for MDR/RR-TB, monitoring patient response to MDR/RR-TB treatment, starting ART in patients on second-line anti-TB regimens and undertaking surgery for patients on MDR-TB treatment.

Two new recommendations that resulted from the 2022 GDG meeting convened by WHO are on the use of new 6-month regimens, dosing of linezolid and the use of modified 9-month regimens.

Access to the new evidence was achieved through close collaboration and engagement with national TB programmes (NTPs), researchers, and a not-for-profit product-development partnership (TB Alliance) investigating the effectiveness and safety of these interventions (see **Web Annex 1**).

Evidence provided for the GDG review on using 6-month novel regimens was from the TB-PRACTECAL trial (evidence on using the regimens BPaLM; bedaquiline, pretomanid, linezolid and clofazimine [BPaLC]; and BPaL), ZeNix trial (evidence on using the BPaL regimen with different dosing schemes for linezolid) and Nix-TB study (evidence on using the BPaL regimen). Evidence on using a new 9-month shorter regimen was from the programmatic data provided by the NTP in South Africa.

In addition, evidence was available on the other treatment regimens that were used as external comparators, to estimate the effectiveness of the intervention regimens. The evidence included data on the use of the WHO-recommended shorter all-oral bedaquiline-containing regimen (data from the programmatic implementation in South Africa) and on the WHO-recommended longer regimens (data from country programmes in Belarus, Georgia, India, Republic of Moldova, Mozambique, Papua New Guinea, the Russian Federation and Somalia); data from fieldwork in multiple countries from Médecins Sans Frontières (MSF); and cohorts from the EndTB project provided by MSF and Partners in Health.

In preparation for the guidelines update, WHO/GTB also received data from another trial – the Newer and Emerging Treatment for MDR/RR-TB (NExT) trial – which was a Phase 2–3 open-label RCT evaluating the effectiveness of an all-oral 6–9-month regimen for the treatment of MDR-TB in South Africa *(21)* in comparison with a local standard of care (SoC) regimen at the time. Sharing of the data by the principal investigator and colleagues at the University of Cape Town and the South African Medical Research Council is gratefully acknowledged. However, during the GDG meeting the panel decided that the data from this study could not be used to complement discussion on the population, intervention, comparator and outcome (PICO) question designed for that study, owing to early termination of the trial and variability of the components in the intervention regimen. This does not undermine the high value of the trial results, which reiterate the inferiority and significantly worse safety profile of the DR-TB regimens based on injectable medicines and fluoroquinolones (but not including new and repurposed drugs). Importantly, the trial showed that better outcomes could be achieved with a 6-month all-oral regimen than with the traditional 9-month or longer injectable-based regimens, supporting the concept of a 6-month all-oral regimen for MDR/RR-TB.

Table B describes the evidence that was generously shared by researchers and NTPs with WHO/GTB. WHO/GTB acknowledges and commends all partners, NTPs and researchers for sharing their data.

Table B. Evidence available for the guidelines update

Trial (setting)	Population	Intervention regimen(s)	Comparator regimen(s)
TB-PRACTECAL trial (South Africa, Belarus, Uzbekistan)	Microbiologically confirmed *M. tuberculosis* in sputum and resistance to rifampicin *The primary analysis population is followed up at 72 weeks.* The number of people reaching 24, 72 and 108 weeks differs because the study was terminated early	Stage 2 (phase 3 trial) 24 weeks BPaLM (B-Pa-$Lzd_{600->300}$-Mfx) Stage 1 (phase 2 trial) 24 weeks BPaLC (B-Pa-$Lzd_{600->300}$-Cfz) 24 weeks BPaL (B-Pa-$Lzd_{600->300}$)	Multiple – local standard of care, including: 9–12-month injectable-containing regimen 18–24-month WHO-recommended regimen (pre-2019) 9–12-month all-oral regimen 18–20-month all-oral regimen
Nix-TB (South Africa)	14 years and older XDR-TB (pre-2021 definition) or treatment intolerant nonresponsive MDR-TB	6–9 month $BPaL_{1200–26}$ Including linezolid 1 200 mg daily for 6 months (option of 9 months for subjects who remain culture positive at month 4)[10]	No standard of care control group
ZeNix (South Africa, Georgia, Moldova and the Russian Federation) *(22)*	14 years and older XDR-TB, pre-XDR-TB (pre-2021 definition) or intolerant/ nonresponsive MDR/RR-TB Stratified by HIV status and type of TB Phase 3 partially blinded	6–9 month BPaL 4 arms with varying linezolid dosing $BPaL_{1200–26\ weeks}$ $BPaL_{1200–9\ weeks}$ $BPaL_{600–26\ weeks}$ $BPaL_{600–9\ weeks}$ Treatment extended if culture positive in weeks 16–26	No standard of care control group
South African TB Program 2019 cohort, EDRWeb (South Africa)	Confirmed rifampicin resistance, based on GeneXpert MTB/RIF or line probe assay	Longer regimen: ≥18 months including bedaquiline, levofloxacin, linezolid, terizidone and clofazimine Shorter regimen including 9–12 months of bedaquiline, linezolid (2 months), levofloxacin, clofazimine, high-dose isoniazid, pyrazinamide and ethambutol	No comparator group

[10] 21 patients in the Nix-TB study received linezolid 600 mg per day, at the beginning of the recruitment period.

Trial (setting)	Population	Intervention regimen(s)	Comparator regimen(s)
South African TB Program 2017 cohort, EDRWeb dataset (South Africa)	Confirmed rifampicin resistance, based on GeneXpert MTB/RIF or line probe assay	Not applicable	Shorter regimen: 9–12 months; 4–6Bdq-Lfx/Mfx-Eto-E-Z-Hh-Cfz), with <1% receiving linezolid
2021 WHO IPD (multiple cohorts following a public call for data by WHO)	Confirmed rifampicin resistance, based upon molecular or culture-based drug susceptibility testing	Not applicable	The WHO IPD was used as an external comparator regimen. Included participants who received 9–12-month all-oral regimens using at least bedaquiline and linezolid; OR used WHO (2019) all-oral bedaquiline-containing regimen (9–12 months) in the combination: 4–6 Bdq(6 m)-Lfx/Mfx-Cfz-Z-E-Hh-Eto / 5 Lfx/Mfx-Cfz-Z-E; OR ≥18-month all-oral treatment regimen containing at least Bdq & Lzd (WHO long)
NExT trial *(21)* (South Africa)	GeneXpert positive MTB and rifampicin resistance on at least two drug susceptibility tests No resistance to fluoroquinolones or second-line injectables Open-label RCT	6–9-month Lzd-Bdq-Lfx-PZA-Eto/high-dose isoniazid/Trd (gene-directed individualized)	**2015–16:** 21–24-month regimen of Km-Mox-PZA-Eto/Hh-Trd for 6–8 months then Mox-PZA-Eth-Trd for 18 months after 2 negative sputum cultures **2016 onwards:** 9–11 Km (6–8) -Mfx-Cfz-Trd-Z-Eto/Hh And longer regimen: 18–20 Km (6–8) -Mfx-Cfz-Trd-Z-Eto/Hh

BPaL: bedaquiline, pretomanid and linezolid; BPaLC: bedaquiline, pretomanid, linezolid and clofazimine; BPaLM: bedaquiline, pretomanid, linezolid and moxifloxacin; HIV: human immunodeficiency virus; IPD: individual patient dataset; *M. tuberculosis; Mycobacterium tuberculosis;* MDR-TB: multidrug-resistant TB; RCT: randomized controlled trial; TB: tuberculosis; WHO: World Health Organization; XDR-TB: extensively drug-resistant TB.

Target audience

These guidelines are primarily targeted at policy-makers in ministries of health, or managers of NTPs who formulate country-specific TB treatment guidelines or are involved in the planning of TB treatment programmes. It is expected that these updated recommendations will also be used by health professionals, including doctors, nurses and educators working in governmental and nongovernmental organizations, and by technical agencies involved in treating patients and organizing treatment services.

Recommendations

Section 1. The 6-month bedaquiline, pretomanid, linezolid and moxifloxacin (BPaLM) regimen for MDR/RR-TB (NEW)

1.1 Recommendation

NEW RECOMMENDATION

No.	Recommendation
1.1	WHO suggests the use of a 6-month treatment regimen composed of bedaquiline, pretomanid, linezolid (600 mg) and moxifloxacin (BPaLM) rather than the 9-month or longer (18-month) regimens in MDR/RR-TB patients. *(Conditional recommendation, very low certainty of evidence)*

Remarks

1. Drug susceptibility testing (DST) for fluoroquinolones is strongly encouraged in people with MDR/RR-TB, and although it should not delay initiation of the BPaLM, results of the test should guide the decision on whether moxifloxacin can be retained or should be dropped from the regimen – in cases of documented resistance to fluoroquinolones, BPaL without moxifloxacin would be initiated or continued.
2. This recommendation applies to the following:
    a. People with MDR/RR-TB or with MDR/RR-TB and resistance to fluoroquinolones (pre-XDR-TB).
    b. People with confirmed pulmonary TB and all forms of extrapulmonary TB except for TB involving the CNS, osteoarticular and disseminated (miliary) TB.[11]
    c. Adults and adolescents aged 14 years and older.
    d. All people regardless of HIV status.
    e. Patients with less than 1-month previous exposure to bedaquiline, linezolid, pretomanid or delamanid. When exposure is greater than 1 month, these patients may still receive these regimens if resistance to the specific medicines with such exposure has been ruled out.
3. This recommendation does not apply to pregnant and breastfeeding women owing to limited evidence on the safety of pretomanid.[12]
4. The recommended dose of linezolid is 600 mg once daily, both for the BPaLM and the BPaL regimen.[13]

[11] See subgroup considerations.

[12] Data on the use of pretomanid in pregnant women are limited. Animal studies do not indicate direct or indirect harmful effects with respect to embryo-fetal development.

[13] Additional details on linezolid dosing and possible dose reductions are given in the implementation considerations.

Rationale

The rationale for this recommendation is based on the evidence and considerations described in detail in the following two subsections. Briefly, data from an RCT (stage 2 of TB-PRACTECAL, corresponds to a phase 3 trial) showed much improved treatment success rates with the BPaLM regimen (89%) of 6 months duration compared with the current SoC regimens (52%), as well as lower levels of treatment failure, death and loss to follow-up. Data from two trials (TB-PRACTECAL and ZeNix) suggested fewer adverse events with a linezolid dose of 600 mg while maintaining high efficacy. It was judged that implementing this regimen was probably feasible and acceptable, with cost–effectiveness and equity probably improved. The comparison of patient groups receiving this regimen with those receiving currently recommended regimens lasting 9 months or longer has favoured the 6-month BPaLM regimen, suggesting it to be the regimen of choice for eligible patient groups.

1.2 Summary of evidence

This section provides the PICO questions posed, the data and studies considered to answer the questions, the methods used for analysis and data synthesis, a summary of evidence on desirable and undesirable effects and certainty of evidence, and a summary of other evidence considered during development of the recommendation. Additional detail on the evidence is available in the web annexes containing the GRADE evidence summary tables (**Web Annex 3**) and GRADE evidence-to-decision tables (**Web Annex 4**).

PICO questions

The recommendation in this section is a result of assessments of the PICO questions listed below. Because of the different intervention and comparator groups used, PICOs 3, 5 and 6 have been split into several sub-PICO questions (details are given in the text and in **Table 1.3**).

PICO question 3–2022 (MDR/RR-TB, 2022): Should BPaL regimens with lower linezolid exposure (dose or duration) be used instead of the original BPaL regimen in patients who are eligible for BPaL regimen?

PICO question 4–2022 (MDR/RR-TB, 2022): Should 6-month regimen using bedaquiline, pretomanid, linezolid be used in patients with pulmonary pre-XDR-TB (MDR/RR-TB with fluoroquinolone resistance)?

PICO question 5–2022 (MDR/RR-TB, 2022): Should 6-month regimen using bedaquiline, pretomanid and linezolid be used in patients with pulmonary MDR/RR-TB and without fluoroquinolone resistance?

PICO question 6–2022 (MDR/RR-TB, 2022): Should 6-month regimen using bedaquiline, pretomanid and linezolid with or without addition of moxifloxacin (BPaLM) or clofazimine be used in patients with pulmonary MDR/RR-TB (with or without fluoroquinolone resistance)?

Data and studies considered

The review of this group of PICO questions during the GDG meeting convened by WHO in February–March 2022 was based on new evidence provided by MSF from the TB-PRACTECAL clinical trial and by the TB Alliance from the ZeNix trial. For several assessments under this PICO question, the data from the 2021 WHO individual patient dataset (IPD) were used. Patient populations included in two trials were recruited following strict inclusion and exclusion criteria; the populations had many similarities and few notable differences. The highlights of the criteria used by these trials are presented in **Table 1.1**. For a complete list of the exclusion criteria, see Annex 2 and published trial protocols.[14]

[14] Available at https://clinicaltrials.gov/ct2/home.

Table 1.1. High-level summary of main inclusion and exclusion criteria: TB-PRACTECAL and ZeNix trials, full lists in Annex 2

	TB-PRACTECAL	ZeNix *(22)*
Inclusion	• Aged 15 years and older • Confirmed TB and RR-TB • Regardless of HIV status	• Aged 14 years and older • Confirmed MDR/RR-TB or pre-XDR-TB • Regardless of HIV status
Exclusion	• Known resistance to Bdq, P, Dlm or Lzd • More than 1 month prior use of Bdq, P, Dlm or Lzd • Pregnant or breastfeeding • Liver enzymes 3 times the upper limit of normal • QTcF >450 ms and other risk factors for QT prolongation (excluding age and gender) or other risk factors for tdp • History of cardiac disease, syncopal episodes, significant symptomatic or asymptomatic arrhythmias (with the exception of sinus arrhythmia) • Moribund • Taking any medications contraindicated with the medicines in the trial • Any baseline laboratory value consistent with Grade 4 toxicity • TB meningoencephalitis, brain abscesses, osteomyelitis or arthritis	• Documented resistance to Bdq, P, Dlm or Lzd • More than 2 weeks of Bdq, Dlm or Lzd • Pregnant • Liver enzymes 3 times the upper limit of normal • BMI <17 • QTcF interval on ECG >500 msec, history of congenital QT prolongation, history of tdp, bradyarrhythmia • Karnofsky score <60 • Peripheral neuropathy of Grade 3–4 • Not expected to survive for more than 6 months • Uncontrolled diabetes or cardiomyopathy, extrapulmonary TB requiring extended treatment, cancer that could affect survival • Abuse of alcohol or illegal drugs • CD4+ count <100 • Use of zidovudine, stavudine or didanosine, use of MAO Inhibitors

Bdq: bedaquiline; BMI: body mass index; Dlm: delamanid; ECG: electrocardiogram; HIV: human immunodeficiency virus; Lzd: linezolid; MAO: monoamine oxidase; MDR/RR-TB: multidrug-resistant or rifampicin-resistant TB; P: rifapentine; QTcF: corrected QT interval by Fredericia; RR-TB: rifampicin-resistant TB; TB: tuberculosis; tdp: torsades de pointes; XDR-TB: extensively drug-resistant TB.

TB-PRACTECAL

TB-PRACTECAL was a multicentre, open-label, multi-arm, randomized, controlled, multistage, Phase 2–3 trial evaluating short treatment regimens containing bedaquiline and pretomanid in combination with existing and repurposed anti-TB drugs (e.g. linezolid and clofazimine) for the treatment of microbiologically confirmed pulmonary MDR/RR-TB.[15]

The study was divided into two stages, with a seamless transition between the stages, meaning that recruitment into an arm would only stop after a decision had been taken following stage 1 primary endpoint data analysis. In the first stage – equivalent to a Phase 2B trial of safety and preliminary efficacy – patients were randomly assigned one of four regimens, stratified by site. Investigational regimens included oral bedaquiline, pretomanid and linezolid. Two of the regimens also included moxifloxacin (arm 1) and clofazimine (arm 2). The main objective of Stage 1 was to select drug

[15] Trial protocol available at https://trialsjournal.biomedcentral.com/articles/10.1186/s13063-022-06331-8.

regimens for evaluation in stage 2, based on 8-week safety and efficacy endpoints. Investigational arms that did not meet predefined safety and efficacy criteria were not considered for further evaluation.

The second stage of the study was equivalent to a Phase 3 trial investigating the safety and efficacy of the most promising regimen. As intended in the study protocol, the regimen was evaluated for safety and efficacy in comparison with the SoC arm at 72 weeks after randomization. Stage 2 of the trial included an intervention arm of BPaLM compared with the locally approved SoC, consistent with WHO recommendations for the treatment of MDR/RR-TB or pre-XDR-TB at the time of trial conduct (including a 9–12-month injectable-containing regimen; 18–24-month WHO-recommended regimen [pre-2019]; 9–12-month all-oral regimen; and 18–20-month all-oral regimen). The TB-PRACTECAL trial stopped enrolling patients soon after its independent data safety and monitoring board indicated that the BPaLM regimen is superior to the SoC, because it was considered that more data were extremely unlikely to change the results of the trial. This trial was not designed to compare the investigational regimens against each other.

Eligible patients were aged 15 years and older, and had bacteriologically (molecular or phenotypic) confirmed TB and resistance to at least rifampicin by a molecular or phenotypic drug susceptibility test. The primary efficacy outcome was the composite endpoint of unfavourable outcomes (failure, death, treatment discontinuation, recurrence or loss to follow-up) at 72 weeks after randomization. Relevant secondary efficacy outcomes included culture conversion at 12 and 24 weeks, unfavourable outcomes at 24 weeks after randomization, unfavourable outcomes at 108 weeks after randomization, median time to culture conversion and recurrence by week 48 in the investigational arms. Participants were randomized in a 1:1:1:1 ratio into either the SoC or one of the following three intervention arms:

- Arm 1: 24 weeks of B-Pa-Lzd-Mfx (BPaLM);
- Arm 2: 24 weeks of B-Pa-Lzd-Cfz (BPaLC); and
- Arm 3: 24 weeks of B-Pa-Lzd (BPaL).

In all intervention arms, linezolid was given at 600 mg daily for 16 weeks then 300 mg daily for the remaining 8 weeks (or earlier when moderately tolerated). Bedaquiline was given at 400 mg once daily for 2 weeks followed by 200 mg three times per week for 22 weeks. Safety monitoring for most participants included multiple electrocardiograms (ECGs) at baseline, then weekly until week 8, every 4 weeks up to week 24 and then every 8 weeks thereafter. Microbiological monitoring included smear microscopy and culture at baseline and day 7, then every 4 weeks up until week 24 and every 8 weeks thereafter.

ZeNix

ZeNix was a Phase 3 partially blinded, randomized trial assessing the safety and efficacy of various doses and treatment durations of linezolid plus bedaquiline and pretomanid in individuals with pulmonary MDR/RR-TB and additional resistance to fluoroquinolones (with or without resistance to injectable agents) or those with treatment intolerant or nonresponsive MDR/RR-TB. Eligible patients were aged 14 years and older, weighed at least 35 kg, had a documented HIV result and had bacteriologically confirmed sputum culture positive XDR-TB (pre-2021 definition) or bacteriologically confirmed MDR/RR-TB, but were treatment intolerant or nonresponsive to previous MDR/RR-TB treatment. The primary study outcome was the incidence of bacteriological failure or relapse or clinical failure through follow-up until 26 weeks after the end of treatment. The secondary outcomes included incidence of bacteriological failure or relapse or clinical failure through follow-up until 78 weeks after the end of treatment. Participants received 26 weeks of treatment with BPaL. Each of the four arms varied the dose and duration of linezolid: 1 200 mg 26 weeks, 1 200 mg 9 weeks, 600 mg 26 weeks or 600 mg 9 weeks. Bedaquiline was given at 200 mg once daily for 8 weeks then 100 mg once daily for 18 weeks. This off-label dosing schedule is supported by pharmacokinetic simulations for an alternative bedaquiline dosing schedule that provides comparable exposures and was developed to support adherence and facilitate treatment administration (all medicines daily throughout the regimen) *(23)*.

Safety monitoring included scheduled testing and assessments of laboratory parameters, ECG, vital signs and other physical examinations *(24)*. Microbiological monitoring included smear microscopy, molecular testing and liquid culture from sputum at baseline and liquid culture at all patient visits thereafter *(24)*.

Table 1.2. Dosing, treatment administration and toxicity-related treatment modification tolerances

TB-PRACTECAL	ZeNix (linezolid 600 mg/26-week arm)
24 weeks	26 weeks, extendable to 39 weeks
Bedaquiline (B) 400 mg once daily for the first 2 weeks of treatment followed by 200 mg 3 times per week for 22 weeks (on-label)	Bedaquiline (B) 200 mg once daily for the first 8 weeks of treatment followed by 100 mg once daily for 18 weeks (off-label)
Pretomanid (Pa) 200 mg once daily for 24 weeks	Pretomanid (Pa) 200 mg once daily for 26 weeks
Linezolid (L) 600 mg daily for 16 weeks then 300 mg daily for the remaining 8 weeks	Linezolid (L) 600 mg daily for 26 weeks (could be reduced to 300 mg)
Treatment administered 7 days a week under direct observation or video-supported therapy	Treatment administered 7 days a week. Adherence was monitored by direct observation or by checking medication cards during site visits
Maximum allowed 2 consecutive weeks of treatment interruption	Maximum allowed total of treatment interruptions – 5 weeks (if 26 weeks duration) and 8 weeks (if 39 weeks duration). All treatment interruptions above 7 consecutive days should have been made up by extending treatment duration. Minimum taken total doses of linezolid – at least 9 weeks

Box 2. Bedaquiline dosing approach in ZeNix trial

A pharmacokinetic simulation study assessed whether a bedaquiline dosing scheme could be devised that would permit daily dosing while maintaining drug exposure levels of the labelled dosing scheme. The key findings from the simulations (23) of the proposed dosing scheme for ZeNix of bedaquiline administered 200 mg daily over 8 weeks followed by 100 mg daily for an additional 16 weeks were as follows:

- The exposures (C_{max}, mean or trough) of the proposed dosing scheme were not expected to exceed the exposures associated with the labelled scheme on Day 14 at the end of the 400 mg daily dose. With the labelled dosing scheme, the highest exposures were on Day 14 at the end of the 400 mg daily loading dose.
- The average daily exposures with the proposed dosing scheme over 6 months were within (or were not substantially different from) the range of exposures over 6 months of the labelled dosing scheme.
- The cumulative exposure, in terms of area under the curve (AUC) over time, is similar between the proposed dosing scheme and the labelled scheme.

2021 WHO IPD

In 2021, WHO issued a public call for data to serve as a comparator group (SoC) against which 6–9-month regimens could be compared. These cohorts received treatment conforming to the WHO DR-TB guidelines of 2020 with bedaquiline and linezolid for a duration ranging from 6 to 24 months. Patients receiving injectable antibiotics were excluded.

Included datasets comprised individuals using one of the following regimens:

- 6–12-month all-oral regimens using at least bedaquiline and linezolid; or
- 9–12-month WHO (2019) all-oral bedaquiline-containing regimen in the combination, such as 4–6 Bdq(6m)-Lfx/Mfx-Cfz-Z-E-Hh-Eto / 5m Lfx/Mfx-Cfz-Z-E; or
- ≥18-month WHO (2018) all-oral treatment regimen containing at least bedaquiline and linezolid.

The individual datasets that are included in this cohort are described in detail in the statistical analysis plan (**Web Annex 6**). To be eligible for inclusion in a short comparator regimen (target 9–12 months at treatment commencement), patients must have fulfilled each of the following:

- had a treatment duration not exceeding 12 months;
- received six or more drugs during treatment, including bedaquiline; and
- if given an outcome of cure or completed, had a treatment duration of 8.5 months or more.

To be eligible for inclusion in a longer comparator regimen (target 18–24 months), patients must have fulfilled each of the following:

- be classified in the dataset as having received a longer regimen (if stated);
- had a treatment duration not longer than 24 months;
- received four or more drugs (regardless of drug susceptibility; i.e. regardless of whether they were likely to be effective), including bedaquiline; and
- if given an outcome of cure or complete, had a treatment duration of 17.5 months or more.

Methods used for analysis and data synthesis

Descriptive analyses of the baseline characteristics of participants in all included studies were performed; characteristics included demographics, diagnostic test results, treatment regimens and treatment outcomes.

Comparative analyses were performed within individual studies and between multiple studies:

- Within study comparisons – for studies in which both a short-course (6 months in duration) regimen and a relevant comparator are used, pairwise comparisons were conducted between each of the short-course regimens and the comparator. For included RCTs (e.g. the TB-PRACTECAL trial and NExT trial), the primary outcome of the prespecified analysis was also calculated and reported.
- Pairwise comparisons between studies – comparisons addressing each PICO question were conducted by comparing outcomes among cohorts in which participants received either the intervention or the control regimen relevant to that question.

Statistical models

For comparisons between dataset or cohorts, outcomes were presented as unadjusted and adjusted risk ratios (RR). Adjusted risk ratios (aRR) were calculated using a log-binomial generalized linear regression (binomial error distribution with log link function). Pre-specified potential confounders were adjusted for using inverse probability propensity score weighting. No convergence issues arose with the log-binomial model. When outcome rates were close to the boundary, aRR were not calculated, and unadjusted RR were presented. For outcomes where the number of outcome events was zero, an unadjusted risk difference (RD) was calculated. For unadjusted RDs or RRs, 95% confidence intervals

(CIs) were calculated using the score method. Covariate selection for calculation of propensity scores was based on data availability and clinical knowledge. The covariates considered for inclusion in the propensity scores analysis included age, gender, baseline smear result, HIV status (including ART status), prior treatment history (including whether previous infection was drug resistant), body mass index (BMI), smoking status, diabetes diagnosis, cavitation at baseline, presence of bilateral disease and fluroquinolone resistance. For the calculation of aRRs, multiple imputation by chain equations using the "within" propensity score approach was used to account for missing data in potential confounders when the proportion of missing values for a confounder was less than 45%.

Timing of follow-up for comparisons between regimens

The analyses undertaken for this evidence review combined results from cohorts with differing follow-up times after initiation of treatment. There were differences in the follow-up time between cohorts (from 5.5 months to 24 months) and within single cohorts (e.g. the WHO IPD 2021 dataset combined multiple cohorts with variable follow-up times). Follow-up time was separated into the time between commencement of treatment and treatment completion, and the period from treatment completion until the end of follow-up. For shorter regimens, post-treatment follow-up was particularly important because higher relapse rates may be a consequence of shorter treatments that do not completely remove *M. tuberculosis*. Where possible, it was important for follow-up time between two groups in a comparison to be equivalent, so that participants had an equivalent likelihood of death or relapse. In these analyses, the follow-up time was measured from the start date of treatment rather than after the date of treatment completion, to minimize the effect of differences in total follow-up time.

The principles for accounting for time periods of follow-up were as follows:

- Where possible, follow up participants in the intervention and control groups for the same total time, so that the likelihood of unsuccessful outcomes (e.g. death) is the same in both groups.
- Limit follow-up to 24 months after treatment initiation for all cohorts. There were no analyses in which both intervention and comparator cohorts had more than 24 months of follow-up available. The evidence accumulated from TB treatment trials demonstrates that a high proportion of recurrences are likely to occur within 12 or even 6 months of stopping treatment *(25)*.
- Select a primary analysis that optimizes the number of participants included in both groups. For shorter (6–9-month regimens), follow-up time in the comparison was included to allow for relapse to be captured.

Additional sensitivity analyses were performed, where possible, evaluating the effect of follow-up time upon treatment outcomes.

Summary of evidence on desirable and undesirable effects and certainty of evidence

The evidence on the novel regimens to inform PICO questions was derived from two trials. It included information on a total of 419 of 423 participants who were enrolled in four arms of the TB-PRACTECAL and on 172 of 181 participants who were enrolled in four arms of the ZeNix trial[16].

Data from patients in relevant arms of these trials were used in each of the comparisons that led to the conclusions and final recommendation on the use of the BPaLM/BPaL regimen. Even though the TB-PRACTECAL trial was not designed to compare the investigational regimens against each other and with the SoC, the comparisons of the different arms of the trial to the BPaLM arm (sub-PICOs 6.2 to 6.6) were performed to aid the panel in making final decisions.

[16] Several participants excluded in each dataset due to unconfirmed rifampicin resistance.

Sub-PICO 3.2

The BPaL 1200–9 arm of the ZeNix trial (where linezolid 1 200 mg daily was used for 9 weeks) was compared with the BPaL 1200–26 arm (where linezolid 1 200 mg daily was used for 26 weeks) in the same population of patients with MDR/RR-TB with or without fluoroquinolone resistance. Primary analysis was undertaken at 12 months post treatment initiation.

Participants with MDR/RR-TB (with or without fluoroquinolone resistance) receiving BPaL with linezolid 1200–9 (*n*=43) compared with participants with the same resistance patterns receiving BPaL with linezolid 1200–26 (*n*=44) experienced:

- lower levels of treatment success (93% vs 98%); that is, a 5% relative reduction (RR=0.95, 95% CI: 0.87 to 1.05);
- higher levels of failure and recurrence (4.7% vs 2.3%); that is, a twofold relative increase (RR=2.1, 95% CI: 0.19 to 22);
- higher levels of deaths (2.3% vs 0%); that is, a 2% absolute increase (RD=0.02, 95% CI: –0.06 to 0.12);
- the same levels of loss to follow-up (0% vs 0%); that is, a 0% absolute difference (RD=0.00, 95% CI: –0.08 to 0.08);
- lower levels of adverse events (16% vs 18%); that is, a 10% relative reduction (RR=0.90, 95% CI: 0.36 to 2.3); and
- the same levels of amplification of drug resistance (0% vs 0%); that is, a 0% absolute difference (RD=0.00, 95% CI: –0.08 to 0.08).

The GDG judged the benefits of BPaL with linezolid 1200–9 to be small and the undesirable effects to be moderate compared with BPaL with linezolid 1200–26. The certainty of evidence was judged to be very low. Based on this, the panel determined that the balance of health effects probably favours BPaL with linezolid 1200–26.

Conclusion

The use of the 26 weeks of 1 200 mg linezolid is suggested over 9 weeks of 1 200 mg linezolid as part of the BPaL regimen in adults with MDR/RR-TB or pre-XDR-TB.

Sub-PICO 3.3

The BPaL 600–26 arm of the ZeNix trial (where linezolid 600 mg daily was used for 26 weeks) was compared with the BPaL 1200–26 arm (where linezolid 1 200 mg daily was used for 26 weeks) in the same population of patients with MDR/RR-TB with or without fluoroquinolone resistance. Primary analysis was undertaken at 12 months post treatment initiation.

Participants with MDR/RR-TB (with or without fluoroquinolone resistance) receiving BPaL with linezolid 600–26 (*n*=43) compared with participants with the same resistance patterns receiving BPaL with linezolid 1200–26 (*n*=44) experienced:

- higher levels of treatment success (100% vs 98%); that is, a 2% relative increase (RR=1.02, 95% CI: 0.98 to 1.07);
- lower levels of failure and recurrence (0% vs 2.3%); that is, a 2% absolute reduction (RD= –0.02, 95% CI: –0.12 to 0.06);
- lower levels of Grade 3–5 adverse events (14% vs 18.6%); that is, a 23% relative reduction (RR=0.77, 95% CI: 0.29 to 2.03); and
- the same levels of deaths (0% vs 0%), loss to follow-up (0% vs 0%) or amplified resistance (0% vs 0%).

The GDG judged the benefits of BPaL with linezolid 600–26 to be moderate and the undesirable effects to be trivial compared with BPaL with linezolid 1200–26. The certainty of evidence was judged to be

very low. Based on this, the panel determined that the balance of health effects probably favours BPaL with linezolid 600–26.

Conclusion

The use of the 26 weeks of 600 mg linezolid over 26 weeks of 1 200 mg linezolid is suggested as part of the BPaL regimen in adults with MDR/RR-TB or pre-XDR-TB.

Sub-PICO 3.4

The BPaL 600–9 arm of the ZeNix trial (where linezolid 600 mg daily was used for 9 weeks) was compared with the BPaL 1200–26 arm (where linezolid 1 200 mg daily was used for 26 weeks) in the same population of patients with MDR/RR-TB with or without fluoroquinolone resistance. Primary analysis was undertaken at 12 months post treatment initiation.

Participants with MDR/RR-TB (with or without fluoroquinolone resistance) receiving BPaL with linezolid 600–9 (*n*=42) compared with participants with the same resistance patterns receiving BPaL with linezolid 1200–26 (*n*=44) experienced:

- lower levels of treatment success (93% vs 98%); that is, a 5% relative reduction (RR=0.95, 95% CI: 0.86 to 1.05);
- higher levels of failure and recurrence (4.8% vs 2.3%); that is, a twofold increase (RR=2.10, 95% CI: 0.20 to 22.26);
- higher levels of loss to follow-up (2.4% vs 0%); that is, a 2% absolute increase (RD=0.02, 95% CI: –0.06 to 0.12);
- lower levels of Grade 3–5 adverse events (14.3% vs 18.2%); that is, a 21% relative reduction (RR=0.79, 95% CI: 0.30 to 2.07); and
- the same levels of deaths (0% vs 0%) or amplified resistance (0% vs 0%).

The GDG judged the benefits of BPaL with linezolid 600–9 to be small and the undesirable effects to be moderate compared with the BPaL with linezolid 1200–26. The certainty of evidence was judged to be very low. Based on this, the panel determined that the balance of health effects probably favours BPaL with linezolid 1200–26.

Conclusion

The use of the 26 weeks of 1 200 mg over 9 weeks of 600 mg linezolid is suggested as part of the BPaL regimen in adults with MDR/RR-TB or pre-XDR-TB.

PICO 3 – Intermediate summary conclusion

The assessment of PICO 3 allowed for the decision on the optimal dosing and duration of linezolid within the BPaLM/BPaL regimen, and narrowed down the subsequent comparisons to the intervention regimen with this particular dose and duration of linezolid – BPaL (600 mg – 26 weeks).

Sub-PICO 4.1

The BPaL 600–26 arm of the ZeNix trial (where linezolid 600 mg daily was used for 26 weeks and the population included patients with MDR/RR-TB with fluoroquinolone resistance) was compared with a cohort of MDR/RR-TB patients with fluoroquinolone resistance from the 2021 IPD who were receiving longer regimens for treatment of MDR/RR-TB, designed in line with 2020 WHO guidelines. Primary analysis was undertaken at 18 months post treatment initiation.

Participants with pulmonary pre-XDR-TB (MDR/RR-TB with fluoroquinolone resistance) receiving BPaL 600–26 (*n*=33) compared with participants receiving longer regimens for MDR/RR-TB (*n*=839) experienced:

- higher levels of treatment success (100% vs 75%); that is, a 34% relative increase (RR=1.34, 95% CI: 1.20 to 1.40);
- lower levels of failure and recurrence (0% vs 6.6%); that is, a 7% absolute reduction (RD= –0.07, 95% CI: –0.08 to –0.04);
- lower levels of deaths (0% vs 9.9%); that is, a 10% absolute reduction (RD= –0.10, 95% CI: –0.12 to –0.01);
- lower levels of loss to follow-up (0% vs 9.1%); that is, a 9% absolute reduction (RD= –0.09, 95% CI: –0.11 to –0.01); higher levels of adverse events (15% vs 4.4%); that is, a 3.4-fold increase (RR=3.44, 95% CI: 1.44 to 8.17); and
- lower levels of amplification of drug resistance (0% vs 7.4%); that is, a 7% absolute reduction (RD= –0.07, 95% CI: –0.09 to –0.03).

The GDG judged the benefits of BPaL with linezolid 600–26 to be large and the undesirable effects to be moderate compared with longer regimens recommended by WHO. The certainty of evidence was judged to be very low. Based on this, the panel determined that the balance of health effects probably favours BPaL with linezolid 600–26.

Conclusion

The use of the 6-month treatment regimen composed of bedaquiline, pretomanid and linezolid (BPaL) rather than a longer (18-month) regimen is suggested in patients with MDR/RR-TB and resistance to fluoroquinolones (pre-XDR-TB), who have either had no previous exposure to bedaquiline and linezolid or have been exposed for less than 1 month.

PICO 4 – Intermediate conclusion

The assessment of PICO 4 resulted in the conditional recommendation for use of the BPaL (600 mg – 26 weeks) regimen over the currently recommended longer regimens in patients with MDR/RR-TB and additional fluoroquinolone resistance (pre-XDR-TB).

Sub-PICO 5.1

The BPaL 600–26 arm of the ZeNix trial (where linezolid 600 mg daily was used for 26 weeks and the population included patients with MDR/RR-TB with or without fluoroquinolone resistance) was compared with a cohort of MDR/RR-TB patients without fluoroquinolone resistance treated in South Africa with the WHO-recommended 9-month regimen with ethionamide for 4 months. Primary analysis was undertaken at 12 months post treatment initiation.

Participants with MDR/RR-TB (with or without fluoroquinolone resistance) receiving the BPaL 600–26 regimen (*n*=43) compared with participants with MDR/RR-TB (without fluoroquinolone resistance) receiving the 9-month regimen with ethionamide (*n*=785) experienced:

- higher levels of treatment success (100% vs 69%); that is, a 45% relative increase (RR=1.45, 95% CI: 1.32 to 1.53);
- lower levels of failure and recurrence (0% vs 1.3%); that is, a 1% absolute reduction (RD=–0.01, 95% CI: –0.02 to 0.07);
- lower levels of deaths (0% vs 19%); that is, a 19% absolute reduction (RD=–0.19, 95% CI: –0.22 to –0.1);
- lower levels of loss to follow-up (0% vs 11%); that is, an 11% absolute reduction (RD= –0.11, 95% CI: –0.14 to –0.03); and

- the same levels of amplified resistance (0% vs 0%); that is, a 0% absolute difference (RD= 0.00, 95% CI: –0.01 to 0.08).

Grade 3–5 adverse events were noted in 14% of participants receiving the BPaL 600–26 but no comparison could be done because no data were available for participants receiving the 9-month regimen with ethionamide.

The GDG judged the benefits of BPaL with linezolid 600–26 to be large and the undesirable effects to be moderate compared with the WHO-recommended 9-month regimen with ethionamide. The certainty of evidence was judged to be very low. Based on this, the panel determined that the balance of health effects probably favours BPaL with linezolid 600–26.

Conclusion

The use of the 6-month treatment regimen composed of bedaquiline, pretomanid and linezolid (BPaL) rather than the 9-month regimen (with ethionamide) is suggested in patients with MDR/RR-TB without resistance to fluoroquinolones, who have either had no previous exposure to bedaquiline and linezolid or have been exposed for less than 1 month.

Sub-PICO 5.2

The BPaL 600–26 arm of the ZeNix trial (where linezolid 600 mg daily was used for 26 weeks and the population included patients with MDR/RR-TB with or without fluoroquinolone resistance) was compared with a cohort of MDR/RR-TB patients without fluoroquinolone resistance from the 2021 IPD, treated with longer regimens for MDR/RR-TB, designed in line with the 2020 WHO guidelines. Primary analysis was undertaken at 18 months post treatment initiation.

Participants with MDR/RR-TB (with or without fluoroquinolone resistance) receiving BPaL 600–26 regimen (*n*=43) compared with participants with MDR/RR-TB (without fluoroquinolone resistance) receiving longer regimens recommended by WHO (*n*=850) experienced:

- higher levels of treatment success (98% vs 74%); that is, a 32% relative increase (RR=1.32, 95% CI: 1.19 to 1.39);
- lower levels of failure and recurrence (2.3% vs 3.3%); that is, a 29% relative reduction (RR=0.71, 95% CI: 0.12 to 3.8);
- lower levels of deaths (0% vs 11%); that is, an 11% absolute reduction (RD= –0.11, 95% CI: –0.13 to –0.03);
- lower levels of loss to follow-up (0% vs 12%); that is, a 12% absolute reduction (RD= –0.12, 95% CI: –0.14 to –0.04);
- higher levels of Grade 3–5 adverse events (14% vs 5%); that is, a fourfold relative increase (aRR=3.99, 95% CI: 1.67 to 9.57); and
- lower levels of amplified resistance (0% vs 2.4%); that is, a 2% absolute decrease (RD= –0.02, 95% CI: –0.04 to 0.06).

The GDG judged the benefits of BPaL with linezolid 600–26 to be large and the undesirable effects to be moderate compared with longer regimens recommended by WHO. The certainty of evidence was judged to be very low. Based on this, the panel determined that the balance of health effects probably favours BPaL with linezolid 600–26.

Conclusion

The use of the 6-month treatment regimen composed of bedaquiline, pretomanid and linezolid (BPaL) rather than longer (18-month) regimens is suggested in patients with MDR/RR-TB and without resistance to fluoroquinolones, who have either had no previous exposure to bedaquiline and linezolid or have been exposed for less than 1 month.

Sub-PICO 5.3

The BPaL 600–26 arm of the ZeNix trial (where linezolid 600 mg daily was used for 26 weeks and the population included patients with MDR/RR-TB with or without fluoroquinolone resistance) was compared with a cohort of MDR/RR-TB patients without fluoroquinolone resistance treated in South Africa with a 9-month regimen with linezolid for 2 months. Primary analysis was undertaken at 12 months post treatment initiation.

Participants with MDR/RR-TB (with or without fluoroquinolone resistance) receiving BPaL with linezolid 600–26 (*n*=43) compared with participants with MDR/RR-TB (without fluoroquinolone resistance) receiving a 9-month regimen with linezolid (*n*=4 216) experienced:

- higher levels of treatment success (100% vs 66%); that is, a 52% relative increase (RR=1.52, 95% CI: 1.38 to 1.55);
- lower levels of failure and recurrence (0% vs 1.2%); that is, a 1% absolute reduction (RD= –0.01, 95% CI: –0.02 to 0.07);
- lower levels of deaths (0% vs 18%); that is, an 18% absolute reduction (RD= –0.18, 95% CI: –0.19 to –0.1);
- lower levels of loss to follow-up (0% vs 15%); that is, a 15% absolute reduction (RD= –0.15, 95% CI: –0.16 to –0.07);
- higher levels of Grade 3–5 adverse events (14% vs 4.9%); that is, a threefold increase (aRR=2.92, 95% CI: 1.38 to 6.18); and
- lower levels of amplified resistance (0% vs 0.6%); that is, a 1% absolute reduction (RD= –0.01, 95% CI: –0.01 to 0.08).

The GDG judged the benefits of BPaL with linezolid 600–26 to be large and the undesirable effects to be moderate compared with receiving a 9-month regimen with linezolid. The certainty of evidence was judged to be very low. Based on this, the panel determined that the balance of health effects probably favours BPaL with linezolid 600–26.

Conclusion

The use of the 6-month treatment regimen composed of bedaquiline, pretomanid and linezolid (BPaL) rather than the 9-month regimen (with linezolid) is suggested in patients with MDR/RR-TB without resistance to fluoroquinolones, who have either had no previous exposure to bedaquiline and linezolid or have been exposed for less than 1 month.

PICO 5 – Intermediate summary conclusion

The three assessments performed under PICO 5 resulted in the conditional recommendations for the BPaL (600 mg – 26 weeks) regimen over the currently recommended 9-month regimen with ethionamide (sub-PICO 5.1), over longer (18-month) regimens (sub-PICO 5.2) and over the new 9-month regimen where ethionamide is replaced with 2 months of linezolid (sub-PICO 5.3) in patients with pulmonary MDR/RR-TB without fluoroquinolone resistance.

Sub-PICO 6.1

The BPaLM regimen arm of the TB-PRACTECAL trial with a population including patients with MDR/RR-TB with or without fluoroquinolone resistance (MDR/RR-TB or pre-XDR-TB) was compared with the comparator arm of the TB-PRACTECAL trial, which comprised MDR/RR-TB or pre-XDR-TB patients treated with multiple local SoC regimens recommended by WHO at the time the trial was conducted (including a 9–12-month injectable-containing regimen, an 18–24-month WHO-recommended

regimen [pre-2019], a 9–12-month all-oral regimen and an 18–20-month all-oral regimen). Primary analysis was undertaken at 72 weeks post treatment initiation.

Participants with MDR/RR-TB (with or without fluoroquinolone resistance) receiving the BPaLM regimen (*n*=62) compared with participants receiving WHO-recommended SoC regimens used in the TB-PRACTECAL trial (*n*=66) experienced:

- higher levels of treatment success (89% vs 52%); that is, a 73% relative increase (aRR=1.73, 95% CI: 1.31 to 2.27);
- lower levels of failure and recurrence (8% vs 26%) that is 74% relative reduction (aRR=0.26, 95%CI 0.10 to 0.71);
- lower levels of deaths (0% vs 3.0%); that is, a 3% absolute reduction (RD= –0.03, 95% CI: –0.10 to 0.03);
- lower levels of loss to follow-up (3.2% vs 20%); that is, a 84% relative reduction (RR=0.16, 95% CI: 0.04 to 0.61);
- lower levels of Grade 3–5 adverse events (21% vs 51%); that is, a 59% relative reduction (aRR=0.41, 95% CI: 0.26 to 0.63); and
- lower levels of amplified resistance (0% vs 1.9%); that is, a 2% absolute reduction (RD= –0.02, 95% CI: –0.07 to 0.02).

The GDG judged the benefits of BPaLM to be large and the undesirable effects to be trivial compared with WHO-recommended SoC regimens. The certainty of evidence was judged to be very low. Based on this, the panel determined that the balance of health effects probably favours the BPaLM regimen.

Conclusion

The use of the 6-month treatment regimen composed of bedaquiline, pretomanid, linezolid and moxifloxacin (BPaLM) rather than a 9-month or longer (18-month) regimen is suggested in MDR/RR-TB patients with or without resistance to fluoroquinolones, who have either had no previous exposure to bedaquiline and linezolid or have been exposed for less than 1 month.

Sub-PICO 6.2

The BPaLM regimen arm of the TB-PRACTECAL trial with a population including patients with MDR/RR-TB with or without fluoroquinolone resistance (MDR/RR-TB or pre-XDR-TB) was compared with the BPaL arm of the TB-PRACTECAL trial, which comprised MDR/RR-TB or pre-XDR-TB patients. Primary analysis was undertaken at 72 weeks post treatment initiation.

Participants with MDR/RR-TB (with or without fluoroquinolone resistance) receiving the BPaLM regimen (*n*=62) compared with participants receiving BPaL in the TB-PRACTECAL trial (*n*=60) experienced:

- higher levels of treatment success (89% vs 77%); that is, a 15% relative increase (aRR=1.15, 95% CI: 0.95 to 1.38);
- lower levels of failure and recurrence (8.1% vs 13%); that is, a 47% relative reduction (aRR= 0.53, 95% CI: 0.17 to 1.63);
- lower levels of loss to follow-up (3.2% vs 10%); that is, a 68% relative reduction (aRR=0.32, 95% CI: 0.08 to 1.34);
- no difference in deaths (0% vs 0%); that is, a 0% absolute difference (RD= 0, 95% CI: –0.06 to 0.06);
- higher levels of Grade 3–5 adverse events (21% vs 20%); that is, a 7% relative increase (aRR=1.07, 95% CI: 0.62 to 1.88); and
- lower levels of amplified resistance (0% vs 2.9%); that is, a 3% absolute reduction (RD= –0.03, 95% CI: –0.08 to 0.01).

The GDG judged the benefits of BPaLM to be moderate and the undesirable effects to be small compared with BPaL. The certainty of evidence was judged to be very low. Based on this, the panel determined that the balance of health effects probably favours BPaLM.

Conclusion

The use of the 6-month treatment regimen composed of bedaquiline, pretomanid, linezolid and moxifloxacin (BPaLM) rather than BPaL is suggested in MDR/RR-TB patients with or without resistance to fluoroquinolones, who have either had no previous exposure to bedaquiline and linezolid or have been exposed for less than 1 month.

Sub-PICO 6.3

The BPaLM regimen arm of the TB-PRACTECAL trial with a population including patients with MDR/RR-TB with or without fluoroquinolone resistance (MDR/RR-TB or pre-XDR-TB) was compared with the BPaLC arm of the TB-PRACTECAL trial that comprised MDR/RR-TB or pre-XDR-TB patients. Primary analysis was undertaken at 72 weeks post treatment initiation.

Participants with MDR/RR-TB (with or without fluoroquinolone resistance) receiving the BPaLM regimen (*n*=62) compared with participants receiving the BPaLC regimen (*n*=64) in the TB-PRACTECAL trial experienced:

- higher levels of treatment success (89% vs 81%); that is, an 11% relative increase (aRR 1.11, 95% CI: 0.94 to 1.31);
- lower levels of failure and recurrence (8.1% vs 9.4%); that is, a 30% relative reduction (aRR= 0.70, 95% CI: 0.2 to 2.29);
- lower levels of deaths (0% vs 1.6%); that is, a 2% absolute reduction (RD= –0.02, 95% CI: –0.08 to 0.04);
- lower levels of loss to follow-up (3.2% vs 7.8%); that is, a 59% relative reduction (RR=0.41, 95% CI: 0.09 to 1.77);
- lower levels of Grade 3–5 adverse events (21% vs 34%); that is, a 39% relative reduction (aRR=0.61, 95% CI: 0.37 to 1.00); and
- lower levels of amplified resistance (0% vs 1.9%); that is, a 2% absolute reduction (RD= –0.02, 95% CI: –0.07 to 0.02).

The GDG judged the benefits of BPaLM to be moderate and the undesirable effects to be trivial compared with BPaLC. The certainty of evidence was judged to be very low. Based on this, the panel determined that the balance of health effects probably favours BPaLM.

Conclusion

The use of the 6-month treatment regimen composed of bedaquiline, pretomanid, linezolid and moxifloxacin (BPaLM) rather than BPaLC is suggested in patients with MDR/RR-TB with or without resistance to fluoroquinolones, who have either had no previous exposure to bedaquiline and linezolid or have been exposed for less than 1 month.

Sub-PICO 6.4

The BPaLC regimen arm of the TB-PRACTECAL trial with population including patients with MDR/RR-TB with or without fluoroquinolone resistance (MDR/RR-TB or pre-XDR-TB) was compared to the comparator arm of the TB-PRACTECAL trial comprised of MDR/RR-TB or pre-XDR-TB patients treated with multiple local SoC regimens recommended by WHO at the time of trial conduct (including a 9–12-month injectable-containing regimen; 18–24-month WHO-recommended regimen [pre-2019];

9–12-month all-oral regimen; and 18–20-month all-oral regimen). Primary analysis was undertaken at 72 weeks post treatment initiation.

Participants with MDR/RR-TB (with or without fluoroquinolone resistance) receiving BPaLC (*n*=64) compared to participants receiving WHO-recommended SoC regimens used in the TB-PRACTECAL trial (*n*=66) experienced:

- higher treatment success (81% vs 52%); that is, a 55% relative increase (aRR=1.55, 95% CI: 1.15 to 2.11);
- lower levels of failure and recurrence (9.4% vs 26%); that is, a 66% relative reduction (aRR=0.34, 95% CI: 0.14 to 0.87);
- lower levels of deaths (1.6% vs 3.0%); that is, a 48% relative reduction (RR=0.52, 95% CI: 0.07 to 3.85);
- lower levels of loss to follow-up (7.8% vs 20%); that is, a 57% relative reduction (aRR=0.43, 95% CI: 0.15 to 1.23);
- lower levels of grade 3 to 5 adverse events (34% vs 51%); that is, a 33% relative reduction (aRR=0.67, 95% CI: 0.46 to 0.97); and
- and higher levels of amplified resistance (1.9% vs 1.9%); that is, a 4% relative increase (RR=1.04, 95% CI: 0.19 to 5.80).

The GDG judged the benefits of BPaLC to be large and the undesirable effects to be trivial compared to WHO-recommended SoC regimens. The certainty of evidence was judged to be very low. Based on this, the panel determined that the balance of health effects probably favours BPaLC.

Conclusion

The use of the 6-month treatment regimen composed of bedaquiline, pretomanid, linezolid and clofazimine (BPaLC) rather than a 9-month or longer (18-month) regimen is suggested in MDR/RR-TB patients with or without resistance to fluoroquinolones, who have either had no previous exposure to bedaquiline and linezolid or have been exposed for less than 1 month (overruled by conclusions of sub-PICO 6.5 and sub-PICO 6.6).

Sub-PICO 6.5

The BPaLC regimen arm of the TB-PRACTECAL trial with a population including patients with MDR/RR-TB with or without fluoroquinolone resistance (MDR/RR-TB or pre-XDR-TB) was compared with the BPaL arm of the TB-PRACTECAL trial that comprised MDR/RR-TB or pre-XDR-TB patients. Primary analysis was undertaken at 72 weeks post treatment initiation.

Participants with pulmonary MDR/RR-TB or pre-XDR-TB receiving BPaLC (*n*=64) compared with participants receiving BPaL 600–300 (*n*=60) experienced:

- higher levels of treatment success (81% vs 77%); that is, a 4% relative increase (aRR=1.04, 95% CI: 0.84 to 1.30);
- lower levels of failure and recurrence (9.4% vs 13%); that is, a 14% relative reduction (aRR=0.86, 95% CI: 0.28 to 2.69);
- higher levels of deaths (1.6% vs 0%); that is, a 2% absolute increase (RD=0.02, 95% CI: –0.05 to 0.08);
- lower levels of loss to follow-up (7.8% vs 10%); that is, a 28% relative reduction (aRR=0.72, 95% CI: 0.21 to 2.47);
- higher levels of adverse events (34% vs 20%); that is, a 64% relative increase (aRR=1.64, 95% CI: 0.97 to 2.79); and
- lower levels of amplification of drug resistance (1.9% vs 2.9%); that is, a 35% relative reduction (RR=0.65, 95% CI: 0.13 to 3.21).

The GDG judged both the desirable and the undesirable effects of BPaLC to be small compared with BPaL. The certainty of evidence was judged to be very low. The balance of health effects did not favour

either the intervention or the comparator; however, taking into consideration the higher cost of the regimen, increased pill burden, reduced acceptability due to skin discolouration and other potential adverse effects related to clofazimine without noticeable net benefit in terms of health effects, the panel judged against the intervention.

Conclusion

The use of the 6-month treatment regimen composed of bedaquiline, pretomanid and linezolid (BPaL) rather than BPaLC is suggested in MDR/RR-TB patients with or without resistance to fluoroquinolones, who have either had no previous exposure to bedaquiline and linezolid or have been exposed for less than 1 month.

Sub-PICO 6.6

The BPaL arm of the TB-PRACTECAL trial with a population including patients with MDR/RR-TB with or without fluoroquinolone resistance (MDR/RR-TB or pre-XDR-TB) was compared with the comparator arm of the TB-PRACTECAL trial that comprised MDR/RR-TB or pre-XDR-TB patients treated with multiple local SoC regimens (including a 9–12-month injectable-containing regimen, an 18–24-month WHO regimen [pre-2019], a 9–12-month all-oral regimen and an 18–20-month all-oral regimen). Primary analysis was undertaken at 72 weeks post treatment initiation.

Participants with MDR/RR-TB (with or without fluoroquinolone resistance) receiving BPaL (*n*=60) compared with participants receiving WHO-recommended SoC regimens used in the TB-PRACTECAL trial (*n*=66) experienced:

- higher levels of treatment success (77% vs 52%); that is, a 47% relative increase (aRR=1.47, 95% CI: 1.09 to 1.99);
- lower levels of failure and recurrence (13% vs 26%); that is, a 48% relative reduction (aRR=0.52, 95% CI: 0.22 to 1.18);
- lower levels of deaths (0% vs 3.0%); that is, a 3% absolute reduction (RD= –0.03, 95% CI: –0.10 to 0.03);
- lower levels of loss to follow-up (10% vs 20%); that is, a 40% relative reduction (aRR=0.60, 95% CI: 0.24 to 1.56);
- lower levels of adverse events (20% vs 51%); that is, a 62% relative reduction (RR=0.38, 95% CI: 0.24 to 0.60); and
- higher levels of amplification of drug resistance (2.9% vs 1.9%); that is, a 59% relative increase (RR=1.59, 95% CI: 0.32 to 7.84).

The GDG judged the benefits of BPaL to be large and the undesirable effects to be trivial compared with WHO-recommended SoC regimens. The certainty of evidence was judged to be very low. Based on this, the panel determined that the balance of health effects probably favours the BPaL regimen.

Conclusion

The use of the 6-month treatment regimen composed of bedaquiline, pretomanid and linezolid (BPaL) rather than a 9-month or longer (18-month) regimen is suggested in patients with MDR/RR-TB with or without resistance to fluoroquinolones, who have either had no previous exposure to bedaquiline and linezolid or have been exposed for less than 1 month.

PICO 6 – Intermediate summary conclusion

The main assessment that defined the overall decision was that of sub-PICO 6.1, which resulted in the conditional recommendation for use of the BPaLM regimen over the internal mix of SoC regimens conforming to the WHO recommendations on 9-month or longer

regimens. The assessments of the investigational regimens against each other and with the SoC in sub-PICOs 6.2–6.6 helped the panel in making final decisions.

Summary of other evidence

Additional data reviewed by the GDG relevant to these PICO questions were a cost–effectiveness analysis, a study on the acceptability and likelihood of implementation of the BPaL regimen, modelled pharmacokinetic data based on the development of a pharmacokinetic toxicodynamic model, and a summary of data on potential reproductive toxicity of pretomanid. No additional research data were available during review of sub-PICO questions 3.2–3.5.

Pharmacokinetic data

Early data from the pharmacokinetics study embedded in the TB-PRACTECAL were presented to the GDG panel in one of the preparatory webinars. The final results of this sub-study were not available at the time of the assessment and could not be fully considered.

The pharmacokinetics of linezolid are highly variable, with efficacy and toxicity dependent on factors such as pathogen susceptibility, drug exposure and the combination of companion drugs. The toxicity of linezolid, especially when used at higher doses and longer durations, is a known phenomenon and various strategies have been suggested to reduce it. However, except for the data available from the ZeNix and TB-PRACTECAL trials, no other strategies have been tested in a trial environment.[17]

Data on reproductive toxicity of pretomanid

New data on the safety of pretomanid based on hormone evaluations in four clinical trials and a paternity survey were assessed; these data have largely alleviated previous concerns about reproductive toxicities observed in animal studies,[18] suggesting that adverse effects on human male fertility are unlikely. A study assessing semen in men undergoing treatment that includes pretomanid is in progress and will address any remaining concerns. Below is a summary of preclinical and clinical data relevant to testicular toxicity of pretomanid:

- rodent toxicology studies – evidence of direct testicular toxicity;
- monkey toxicology studies – no evidence for direct testicular toxicity; abnormal sperm findings considered to be secondary to declining physical condition;
- hormone data from clinical studies – no changes in follicle stimulating hormone (FSH), luteinizing hormone (LH) and inhibin B, consistent with testicular toxicity;
- paternity survey – 44 children fathered by 38 men (12%) who participated in pretomanid studies of 4–6 months treatment duration; and
- semen study – ongoing study evaluating semen in men undergoing pretomanid treatment.

Resources required and cost–effectiveness

Estimated regimen costs (in adults) at Global Drug Facility (GDF) prices[19] are about US$ 688 for BPaL (600–26), US$ 716 for BPaLM (600–26), an average of US$ 771 for longer regimens (depends on length and composition) and US$ 535–557 for 9-month regimens. Data from three studies were available on more detailed analyses of resources required and cost–effectiveness; two of these studies compared the BPaL regimen with longer (18-month) regimens *(26, 27)* and one compared the BPaL, BPaLM and BPaLC regimens with longer (18-month) regimens and with the 9-month regimen with

[17] As presented in the expert review (by Dr J-W. Alffenaar, University of Sydney) to the GDG panel in one of the preparatory webinars.

[18] Pretomanid has been shown to cause testicular atrophy and impaired fertility in male rats.

[19] Estimated regimen prices were calculated using the average weighted price for each medicine (average weighted price accounts for the different prices for each supplier of that medicine weighted by the market share allocation received from each GDF tender), the duration indicated (in months) and assuming 30 days of treatment per month. Actual final costs may differ based on the products delivered.

ethionamide *(28)*. The applicability of the results from these studies varied by PICO and sub-PICO question, and the panel noted associated caveats when discussing these results (details available in the GRADE evidence-to-decision tables in **Web Annex 4**). Overall, based on these three publications, estimates for comparative total cost (drugs and delivery) within country appear to be between 1.4-fold and 6-fold higher (longer regimens) or 1–18% higher (9-month regimens) than for BPaLM/BPaL. Thus, the panel judged that implementation of BPaLM/BPaL would probably to lead to large savings when replacing the longer (18-month) regimens and moderate savings when replacing the 9-month regimens.

The cost–effectiveness study *(28)* found that, in most settings, BPaLM/BPaL is cost saving, mainly because of reduced time in care and therefore reductions in numbers of outpatient visits, inpatient bed-days and laboratory tests. The panel judged that cost–effectiveness probably favours BPaLM/BPaL.

Equity, acceptability and feasibility

The panel considered the treatment duration and the ability to decentralize treatment (to enable access for remote, underserved settings and disadvantaged populations) to affect equity. Despite not being able to identify relevant research evidence, the panel used their collective experience to judge that there would probably be advantages associated with the use of the BPaLM/BPaL regimen owing to its reduced complexity and shorter duration. Therefore, the panel judged that use of the BPaLM/BPaL regimen would probably increase equity.

A study on the acceptability and feasibility of the BPaL regimen from the provider perspective *(29)* was considered to be relevant evidence for the assessment of BPaL and indirectly for the assessment of BPaLM. This was a mixed-methods study among a cross section of health care workers, and programmatic and laboratory stakeholders that was carried out between May 2018 and May 2019 in Indonesia, Kyrgyzstan and Nigeria. The results from this study suggested that acceptability and feasibility overall were high. BPaL was rated as acceptable by more than 80% of participants across domains and stakeholders and 88% of interviewed stakeholders stated that they would probably implement BPaL once it became available. Stakeholders appreciated that BPaL would reduce the workload and financial burden on the health care system; expressed concerns about BPaL safety (monitoring), long-term efficacy and national regulatory requirements; and stressed the importance of addressing current health systems constraints, especially in treatment and safety monitoring systems. Results from a second qualitative study *(30)* with a focus on the patient perspective were presented to the panel; this study suggested that patients would welcome the positive impact of shorter treatment on employment status.[20]

The panel noted these study results and, as part of their deliberations, they considered patients and health care providers as key stakeholders. The panel considered the following aspects to be critical with regard to the acceptability of BPaLM/BPaL: regimen duration and drug-safety monitoring needs (relating both to the necessary travel, loss of income and general disruption of the life of patients, and to workload for the health care system), and the need for DST. The panel judged that the BPaLM/BPaL regimen would probably be acceptable. Regarding feasibility, the panel noted the limited availability of pure substances of drugs in the BPaLM/BPaL regimen for use in DST as a potential barrier to implementation; they also noted that data on the critical concentration of pretomanid for use in DST are limited. However, given the reduced duration, complexity and associated workload of BPaLM/BPaL, the panel judged that implementation of BPaLM/BPaL is probably feasible.

1.3 Evidence to recommendations: considerations

Based on the decisions taken during the review and the combination of assessments described above, the new recommendation is to use the BPaLM regimen as the first choice in the defined patient group with MDR/RR-TB, with the regimen to be used under routine programmatic conditions. Patients with

[20] Unpublished, courtesy of Beverley Stringer, Manson unit, Médecins Sans Frontières.

MDR/RR-TB who are not eligible for this regimen can be treated using one of the 9-month regimens (see **Section 2**). The use of the longer regimen is reserved (see **Section 3**) for individuals with MDR/RR-TB and fluoroquinolone resistance with further resistance or intolerance to bedaquiline, linezolid (XDR-TB) or pretomanid, who would then receive a longer regimen designed with remaining effective medicines from Groups A, B and C, according to their drug susceptibility profile and other parameters.

Table 1.3 lists the comparisons and decisions on each of the sub-PICO-questions that were eventually used by the GDG to conclude with this summary recommendation. Throughout the discussion, the GDG panel focused on direct (within trial) comparisons among the TB-PRACTECAL trial arms, to ensure consistency and because it was felt that results based on random allocation to interventions were far more reliable than indirect, nonrandomized comparisons. Whereas the certainty of evidence of these (TB-PRACTECAL-internal) comparisons was still judged to be very low, the panel deemed it to be higher than that of other (indirect or between-trial or cohort) comparisons.

Although assessments of PICO questions 3, 4, 5 and 6 have all contributed to the summary recommendation, the main assessment that defined the overall decision was that of sub-PICO 6.1 on the comparison of the BPaLM regimen of the stage 2 (corresponds to Phase 3) in the TB-PRACTECAL trial with the mix of SoC regimens (conforming to the WHO-recommended 9-month or longer regimens). Even though the TB-PRACTECAL trial was not designed to compare the investigational regimens against each other and with the SoC, the comparisons of the different arms of the trial with the BPaLM arm (sub-PICOs 6.2–6.6) were performed to aid the panel in making final decisions.

The assessment of PICO 3 allowed for the decision on the optimal dosing and duration of linezolid within the BPaLM/BPaL regimen and narrowed down the subsequent comparisons to the intervention regimen with this particular dose and duration of linezolid – BPaL (600 mg – 26 weeks). The justification for how the other assessments have contributed to the overall recommendation can be summarized as follows:

a. **The assessment of PICO 4 resulted in the conditional recommendation for use of BPaL (600 mg – 26 weeks) regimen over the currently recommended longer regimens in patients with MDR/RR-TB and additional fluoroquinolone resistance.**
b. **The three assessments performed under PICO 5 resulted in the conditional recommendations for the BPaL (600 mg – 26 weeks) regimen over the currently recommended 9-month regimen with ethionamide (sub-PICO 5.1), over longer regimens (sub-PICO 5.2) and over the new 9-month regimen where ethionamide is replaced with 2 months of linezolid (sub-PICO 5.3) in patients with pulmonary MDR/RR-TB without fluoroquinolone resistance.**
c. **The assessment of sub-PICO 6.1 resulted in the conditional recommendation for use of the BPaLM regimen of the TB-PRACTECAL trial over the comparator, the mix of SoC regimens under this trial conforming to the WHO recommendations on 9-month or longer regimens, depending on the trial site.**
d. **The assessments of sub-PICOs 6.4 and 6.6 resulted in the conditional recommendations for BPaLC and BPaL over the SoC in the TB-PRACTECAL trial; thus all three 6-month BPaL-based regimens were assessed to be preferred over the mix of SoC regimens under this trial.**
e. **The assessments of sub-PICOs 6.3 and 6.5 resulted in the conditional recommendations for BPaLM and BPaL over BPaLC; based on these assessments the GDG concluded that BPaLC should *not* be recommended as a regimen.**
f. **The assessment of sub-PICO 6.2 resulted in the conditional recommendations for BPaLM over BPaL; thus, it highlighted the use of the BPaLM regimen as the preferred regimen under the conditions specified in the recommendation and remarks. Compared with BPaL, BPaLM led to more treatment success, fewer failures or recurrences and less emerging drug resistance while showing little difference in adverse events.**

Table 1.3. PICO questions and decisions of the GDG panel

#	PICO	Population	Intervention	Comparator [data source]	Sub-PICO	Recommendation
3	Should BPaL regimens with lower linezolid exposure (dose or duration) be used instead of the original BPaL regimen in patients who are eligible for BPaL regimen?	MDR/RR-TB or pre-XDR-TB	BPaL (1 200 mg – 9 weeks)	BPaL 1200–26 [ZeNix][a]	3.2	Conditional against the intervention
			BPaL (600 mg – 26 weeks)		3.3	Conditional for the intervention
			BPaL (600 mg – 9 weeks)		3.4	Conditional against the intervention
			BPaL (600 mg then 300 mg)		3.5	No recommendation because the panel felt that comparison of data from different trials was less reliable and indirect
4	Should a 6-month regimen using bedaquiline, pretomanid and linezolid be used in patients with pulmonary pre-XDR-TB (MDR/RR-TB with fluoroquinolone resistance)?	Pre-XDR-TB	BPaL (600 mg – 26 weeks) (FQ-res only)	Longer regimens [IPD][b]	4.1	Conditional for the intervention
5	Should a 6-month regimen using bedaquiline, pretomanid and linezolid be used in patients with pulmonary MDR/RR-TB and without fluoroquinolone resistance?	MDR/RR-TB	BPaL (600 mg – 26 weeks) (FQ-res and FQ-susc)	9-month (Eto)	5.1	Conditional for the intervention
				Longer regimens [IPD][b]	5.2	Conditional for the intervention
				9-month (Lzd)	5.3	Conditional for the intervention

#	PICO	Population	Intervention	Comparator [data source]	Sub-PICO	Recommendation
6	Should a 6-month regimen using bedaquiline, pretomanid and linezolid with or without addition of moxifloxacin (BPaLM) or clofazimine be used in patients with pulmonary MDR/ RR-TB (with or without fluoroquinolone resistance)?	MDR/RR-TB or pre-XDR-TB	BPaLM	Mix of 9-month and longer regimens [TB-PRACTECAL][c]	6.1	Conditional for the intervention
			BPaLM	BPaL (600 mg then 300 mg) [TB-PRACTECAL][c]	6.2	Conditional for the intervention
			BPaLM	BPaLC [TB-PRACTECAL][c]	6.3	Conditional for the intervention
			BPaLC	Mix of 9-month and longer regimens [TB-PRACTECAL][c]	6.4	Conditional for the intervention
			BPaLC	BPaL (600 mg then 300 mg) [TB-PRACTECAL][c]	6.5	Conditional against the intervention
			BPaL (600 mg then 300 mg)	Mix of 9-month and longer regimens [TB-PRACTECAL][c]	6.6	Conditional for the intervention

BPaL: bedaquiline, pretomanid and linezolid; BPaLC: bedaquiline, pretomanid, linezolid and clofazimine; BPaLM: bedaquiline, pretomanid, linezolid and moxifloxacin; Eto: ethionamide; FQ-res: fluoroquinolone resistant; FQ-susc: fluoroquinolone susceptible; GDG: Guideline Development Group; IPD: individual patient data; Lzd: linezolid; MDR/RR-TB: multidrug-resistant or rifampicin-resistant TB; PICO: population, intervention, comparator and outcome; TB: tuberculosis; XDR-TB: extensively drug-resistant TB.

[a] ZeNix trial.

[b] 2021 IPD.

[c] TB-PRACTECAL.

The GDG panel discussed the subgroups and implementation considerations, and the monitoring and evaluation and research priorities as they pertain to the summary recommendation rather than for each individual sub-PICO question.

1.4 Subgroup considerations

Children

Children were excluded from the ZeNix trial (aged 0–13 years) and the TB-PRACTECAL trial (aged 0–14 years); therefore, no analysis specific to this subgroup of patients could be performed. All medicines in the BPaLM regimen have been used in children except for pretomanid. New data on bedaquiline has been recently reviewed and its use has been expanded to all ages (see additional recommendation in **Section 3** and *(31)*). The lack of safety data on pretomanid in children aged below 14 years was the main barrier for potential extrapolation of the BPaLM/BPaL recommendation to the threshold of being aged below 14 years. Thus, the recommendation of the BPaLM/BPaL regimen applies to adults and adolescents aged 14 years and older.

People living with HIV

HIV was diagnosed in 34 of 172 (19.8%) people enrolled in the ZeNix trial; however, it was impossible to perform any adjusted stratified analyses for people living with HIV (PLHIV), owing to the small sample size in sub-PICO comparisons 3.2, 3.3, 3.4 and 3.5. PLHIV were eligible for enrolment in the ZeNix trial if they had a CD4 count of more than 100 cells/mm^3 and if they were using antiretroviral medications.[21] No aspects specific to HIV status or CD4 count were in the list of TB-PRACTECAL exclusion criteria, and PLHIV represented 27% of those enrolled. The median CD4 count among PLHIV was 322 (interquartile range [IQR] 217–622) across the four arms.

It is important to take drug–drug interactions into account when administering TB and HIV medications in combination; such interactions are discussed below. Although some therapies are to be avoided, there are alternative antiretroviral agents that can be considered when pretomanid is used. Thus, the recommendation of the BPaLM/BPaL regimen applies to all people regardless of HIV status, although some caution should be used when enrolling patients with CD4 counts lower than 100 cells/mm^3.

Pregnant and lactating women

Pregnant and lactating women were excluded from the ZeNix and TB-PRACTECAL trials owing to unknown effects of the new medicine, pretomanid, on fetal development; therefore, no analysis specific to this subgroup of patients could be performed. The use of bedaquiline in pregnancy has been associated with infants born with a lower mean birth weight than infants whose mothers did not take bedaquiline; however, when infants were followed up over time, no evidence of late adverse impacts was found (see **Section 3.2**). Breastfeeding is not recommended for women taking pretomanid *(32)*. Thus, the recommendation of the BPaLM/BPaL regimen does not apply to pregnant and breastfeeding women. While the safety of pretomanid during pregnancy and breastfeeding is unclear, other treatment options need to be used.

Extrapulmonary TB

Patients with extrapulmonary TB were excluded from the ZeNix and TB-PRACTECAL trials; therefore, no analysis specific to this subgroup of patients could be performed. The available data on the central nervous system (CNS) penetration of bedaquiline or pretomanid are limited. Although all

[21] In the ZeNix trial, permitted antiretroviral treatments were nevirapine in combination with any nucleoside reverse transcriptase inhibitors (NRTIs); lopinavir/ritonavir in combination with any NRTIs; tenofovir/lamivudine/abacavir (if normal renal function); triple NRTI therapy consisting of zidovudine, lamivudine and abacavir (noting the increased risk of peripheral nerve toxicity with zidovudine and linezolid); and raltegravir in combination with NRTIs.

forms of extrapulmonary TB were excluded from the clinical trials, the GDG felt that extrapolation to extrapulmonary TB and other forms of TB was warranted except in cases involving severe forms of TB that may require special treatment arrangements and decisions, particularly TB involving the CNS, osteoarticular and disseminated forms of TB. Thus, the recommendation of the BPaLM/BPaL regimen applies to people with pulmonary TB and all forms of extrapulmonary TB except for TB involving the CNS, and osteoarticular and disseminated (miliary) TB.

Other considerations

Several other groups of patients were excluded from the two trials; for example, patients with liver enzyme measurements three or more times over the upper limit of normal; people with a corrected QT interval by Fredericia (QTcF) more than 500 ms, or history of cardiac disease, syncopal episodes, significant arrythmias, congenital QT prolongation, torsade de pointes or cardiomyopathy; those with a current peripheral neuropathy of Grade 3–4; and moribund patients with very low BMI (<17). These groups of patients may only receive the regimen if the treating physician judges this to be the best option despite these contraindications.

1.5 Implementation considerations

High treatment success rates shown for the BPaLM and BPaL regimens in the Nix-TB study and in the ZeNix and TB-PRACTECAL trials, and favourable comparison with the current SoC regimens led to thorough discussions during the GDG meeting of an overall recommendation for implementation under routine programmatic conditions and of the implementation considerations for this regimen. Given that this recommendation is conditional, the results of additional or ongoing operational research will help to add further knowledge that can be used to adjust and improve implementation guidance for the regimen.

Patient selection

Overall, to reproduce the treatment success rates observed in the ZeNix and TB-PRACTECAL trials, it is important to carefully select eligible patients. Once those patients are enrolled, it is also important to provide effective patient support to enable adherence to treatment. It is also important to maintain close monitoring for adverse events, response to treatment and emerging drug resistance, and to properly manage adverse drug reactions and prevent complications from drug–drug interactions.

The selection of patients is best aligned with the eligibility criteria of two trials (also reflected in the subgroup consideration above). The patients that can be enrolled on the BPaLM/BPaL regimen should have bacteriologically confirmed MDR/RR-TB, with or without resistance to fluoroquinolones.

Drug susceptibility testing

It is important to pay attention to the previous use and susceptibility status of the medicines comprising this regimen. Patients with a known history of more than 1 month use of bedaquiline, pretomanid (or delamanid, given some degree of cross-resistance) and linezolid should not be enrolled on this regimen, unless the results of recent DST of these medicines has confirmed susceptibility. In cases where there is no prior use of these medicines or confirmed susceptibility, fluoroquinolone resistance testing should also be done before the start of treatment. However, fluoroquinolone resistance testing should not delay treatment initiation (e.g. in cases where this DST is not available or results are delayed). When DST results confirm fluoroquinolone susceptibility, treatment can be continued without any modifications. **In cases of fluoroquinolone resistance, moxifloxacin should be dropped and the regimen continued as the BPaL combination only.** This modification may seem counterintuitive, because patients with TB that is resistant to an increased number of drugs will receive fewer TB medicines. However, moxifloxacin is unlikely to provide a benefit in the presence

of fluoroquinolone resistance and the BPaL regimen has been shown to have high efficacy without moxifloxacin. In the context of fluoroquinolone resistance, omitting moxifloxacin will help to avoid potential toxicity related to this medicine. Conversely, in the absence of fluoroquinolone resistance, the use of moxifloxacin further increases the efficacy of the regimen and may provide protection against acquired bedaquiline resistance, and thus is recommended. If fluoroquinolone DST results are unavailable, the GDG judged the likely benefits of retaining moxifloxacin as part of the regimen as outweighing the potential harms; therefore, WHO suggests using the BPaLM regimen in this situation.

The establishment and strengthening of DST services is a vital consideration for implementation of all treatment regimens for MDR/RR-TB. In patients with bacteriologically confirmed MDR/RR-TB, the Xpert® MTB/XDR (Cepheid) or GenoType® MTBDR*sl* (Hain Lifescience) assays may be used as the initial test, in place of culture and phenotypic DST, to detect resistance to fluoroquinolones *(33, 34)*. If testing for susceptibility to bedaquiline or linezolid is available, it is highly desirable to also carry this out at baseline and in the absence of culture conversion during treatment. DST for pretomanid is not yet available; however, WHO expects to set critical concentrations for phenotypic DST in the next update of the technical report on critical concentrations for DST of medicines used in the treatment of DR-TB *(35)*.

Currently, there is limited capacity globally for DST for bedaquiline and linezolid. As these medicines and regimens containing these medicines become more widely used, laboratory capacity in this area must be strengthened. National and reference laboratories will need to have necessary facilities and reagents to make DST available; also, they will need data on the minimum inhibitory concentration (MIC) distribution of all *M. tuberculosis* lineages that are circulating globally. Establishing or expanding capacity for sequencing of *M. tuberculosis* can provide a strong and future-proof platform for DST. If resistance to any of the component medicines in the BPaL regimen is detected, treatment with another recommended regimen should be started. The WHO TB Supranational Reference Laboratory (SRL) Network is available to support national TB reference laboratories in performing quality-assured DST. A WHO technical consultation in 2017 established critical concentrations for DST for the fluoroquinolones, bedaquiline, delamanid, clofazimine and linezolid *(35)*. Methods for testing pretomanid susceptibility are currently under development. When methods for DST are available, countries will need to add surveillance of resistance to new medicines to their routine efforts or surveys. These data can guide the adoption and use of new regimens and can also protect against amplification of resistance profiles.

Drug–drug interactions

It is important to take drug–drug interactions into account when administering TB and HIV medications in combination, including the documented interactions between bedaquiline and efavirenz *(36)*. Efavirenz reduces pretomanid exposures significantly; therefore, an alternative antiretroviral agent should be considered if pretomanid forms part of the BPaLM/BPaL regimen *(32)*. The preferred ART regimens for co-administration with BPaLM/BPaL are dolutegravir-based regimens in combination with two nucleoside reverse transcriptase inhibitors.

The following medications should be avoided or may require additional precautions during treatment with BPaLM/BPaL:

- efavirenz;
- drugs known to significantly prolong the QTc interval, including neuroleptics-phenothiazines (e.g. thioridazine, haloperidol, chlorpromazine, trifluoperazine, pericycline, prochlorperazine, fluphenazine, sertindole and pimozide), ondansterone, quinoline antimalarials (e.g. halofantrine, chloroquine, hydroxychloroquine and quinacrine), anti-arrhythmic drugs (e.g. quinidine, procainamide, encainide, disopyramide, amiodarone, flecainide and sotalol) and fluoroquinolones other than those included in the trial regimens;

- strong CYP3A4 inducers (e.g. phenytoin, carbamazepine, phenobarbital, St. John's wort [Hypericum perforatum], rifamycins, and systemic, multiple dosing of dexamethasone)
- strong CYP3A4 inhibitors (e.g. azole antifungals: ketoconazole, voriconazole, itraconazole and ketolides such as telithromycin; and macrolide antibiotics other than azithromycin) for more than 2 weeks;
- monoamine oxidase inhibitors (phenelzine, isocarboxazid and tranylcypromine); and
- drugs known to induce myelosuppression (e.g. azathioprine and cytotoxic agents).

Care and support

Treatment administration coupled with support to patients can boost adherence and ensure optimal drug effectiveness and safety. Measures to support patient adherence (e.g. by facilitating patient visits to health care facilities or home visits by health care staff, or by using digital technologies for daily communication) may be important to retain patients on treatment, even when a regimen is comparatively short *(37)*. WHO recommendations on care and support and a related handbook are available on the web under the *WHO consolidated guidelines on tuberculosis. Module 4: Treatment – tuberculosis care and support (38)*.

Active TB drug-safety monitoring and management

Close monitoring of adverse effects of treatment is particularly important for the shorter treatment regimens and for regimens including new medicines (e.g. this regimen includes a novel compound – pretomanid), to ensure relapse-free cure. Active pharmacovigilance and proper management of adverse drug reactions and prevention of complications from drug–drug interactions will ensure proper patient care; and reporting any adverse drug reactions to the responsible drug-safety authority in the country will inform national and global policy *(39)*. Additional information about active TB drug-safety monitoring and management (aDSM) is available in the operational handbook.

Regimen composition, dosing of component medicines and frequency

The BPaLM/BPaL regimen consists of bedaquiline, pretomanid and linezolid, with or without moxifloxacin throughout the regimen duration. Pretomanid is administered at 200 mg once daily for the duration of the regimen. When moxifloxacin is part of the regimen, it is dosed at 400 mg once daily throughout the treatment course. The fluoroquinolone of choice used in the TB-PRACTECAL trial was moxifloxacin; given that no evidence on using other fluoroquinolones was available at the time of the GDG assessments, the replacement of moxifloxacin with levofloxacin or any other fluoroquinolone cannot be recommended at this stage. The frequency of dosing should be 7 days a week with treatment support or using video-supported therapy; that is, as it was administered in both the trials.

Bedaquiline dosing schemes

The TB-PRACTECAL and ZeNix trials used slightly different dosing schemes for bedaquiline although the overall drug exposure was comparable *(23)*. The dosing schedule used in the TB-PRACTECAL trial was consistent with the product label whereas the dosing schedule used in the ZeNix trial presented the advantage of daily dosing throughout the regimen and may be used as one of the options for administration. Either of the bedaquiline dosing schemes may be used for programmatic implementation:

- daily throughout treatment: 200 mg once daily for 8 weeks followed by 100 mg once daily; and
- daily for loading dose and three times per week thereafter: 400 mg once daily for 2 weeks followed by 200 mg three times per week.

Dosing of linezolid

The ZeNix trial used several different dosing and duration schemes of linezolid, with the aim of determining the optimal administration schedule for this medicine. Linezolid is known to cause several potentially serious adverse effects; among those of most concern are peripheral neuropathy, optic neuritis and myelosuppression *(40)*. The GDG review of the ZeNix trial data identified the optimal dosing for linezolid to be 600 mg once a day for 26 weeks, and this arm of the ZeNix trial was used for the main comparisons. Study participants in this arm of the trial received 600 mg of linezolid once daily for 26 weeks, with a reduction to 300 mg daily allowed in the event of linezolid specific toxicities. In the TB-PRACTECAL trial, dosing of linezolid was slightly different – participants were given 600 mg daily for 16 weeks and then 300 mg daily for the remaining 8 weeks (the duration of BPaLM in this trial was 24 weeks).

The GDG panel considered that it would be preferable to use linezolid 600 mg/daily throughout the regimen, but the dose can be reduced to 300 mg/daily if necessary to mitigate toxicity.

Regimen duration, changes and extensions

The BPaLM and BPaL regimens have been studied as the standardized courses of treatment. Therefore, modification of the regimen through early discontinuation or replacement of any of the component medicines may result in different (and possibly worse) treatment outcomes. In the TB-PRACTECAL trial, patients received 24 weeks of BPaLM. In the ZeNix trial, treatment was extended to a total of 9 months in patients on the BPaL regimen who remained sputum culture positive or who reverted to being sputum culture positive between months 4 and 6, or whose clinical condition suggested they may have progressive TB. In cases where treatment was interrupted and treatment duration was extended to make up for missed doses, it was necessary for patients to complete 6 months of the regimen (i.e. 26 weeks of prescribed doses) within 8 months; also, for patients in whom treatment was extended, it was necessary to complete 9 months of treatment (i.e. 39 weeks of prescribed doses) within 12 months.

Eligible patients with susceptibility to fluoroquinolones can be started on the BPaLM regimen for 6 months, with dosing of individual medicines as described above. This combination of medicines can be continued throughout the regimen without any prolongation (unless there is a need to make up the missed doses). In cases where resistance to fluoroquinolones is identified before or after treatment initiation, moxifloxacin can be discontinued. When the regimen is BPaL from the start or is changed to BPaL, it can be extended to a total of 39 weeks (counting from the start of the therapy with BPaLM/BPaL). This extension is justified in cases of failure to convert culture between months 4 and 6 while on treatment; alternatively, it can be based on the clinical judgement of the treating physician. Up to 1 month can be added to the overall treatment duration if there is a need to make up the missed doses.

The GDG panel acknowledged these slight differences in the treatment duration of the BPaLM and BPaL regimens as studied in these two trials, and suggested standardizing the treatment duration of BPaLM to 6 months (26 weeks) during programmatic implementation; for BPaL they suggested the possibility of extension to a total of 9 months (39 weeks) if sputum cultures are positive between months 4 and 6. All medicines in the regimen are to be used throughout treatment duration, including a potential extension from 26 to 39 weeks (when BPaL is used). Ideally, missing doses of all three or four drugs in the regimen should be avoided; however, if doses are missed, any interruption of longer than 7 days should be made up by extending the treatment duration (for the number of missed doses); therefore, 26 or 39 weeks of prescribed doses should be completed within an overall period of 7 or 10 months, respectively.

Missing doses and tolerances for treatment interruptions

The TB-PRACTECAL and ZeNix trials used different tolerances for treatment interruption and missing doses, and the ZeNix trial protocol provided specific rules for linezolid administration.

The GDG panel suggested standardizing the allowable missing doses and the approach to linezolid administration. The following pragmatic approach is suggested to guide clinical judgement and potential minor deviations in individual cases:

- all possible efforts should be made to support the patient and manage the adverse events to ensure uninterrupted treatment and intake of all medicines in the regimen; however, when medicine cannot be tolerated it should be stopped;
- consecutive treatment interruption (of all medicines in the regimen) of up to 2 weeks should be made up and added to the treatment duration;
- nonconsecutive missed doses of all medicines in the regimen up to a cumulative total of 4 weeks should be made up and added to the treatment duration; and
- after consecutive administration of linezolid at recommended doses (600 mg/daily) for at least 9 weeks, in case of intolerability the dose can either be adjusted down (to linezolid 300 mg/daily) or omitted (while other medicines in the regimen are continued) for a total of a maximum of 8 weeks throughout the treatment course.

In case any single one of these tolerances is exceeded, a thorough assessment of the patient's status will be required to decide whether to continue the treatment strategy or modify it.

1.6 Monitoring and evaluation

Patients who receive BPaLM/BPaL need to be tested at baseline and then monitored during treatment using schedules of relevant clinical and laboratory testing. If feasible, it is also important to follow up patients 12 months after the completion of treatment for possible relapse, including with sputum culture and smear.

The bacteriological status of the patient should be available before treatment initiation, with confirmation of TB disease and rifampicin resistance as a minimum if possible. It is recommended to monitor patients with MDR/RR-TB while on treatment using monthly sputum cultures. Failure to convert sputum culture at or after the fourth month on treatment is a potential sign of a failing treatment regimen. The DST for fluoroquinolones is important to support prescription of the relevant combination, BPaLM or BPaL, to maximize the efficacy and prevent unnecessary potential toxicity. Country programmes are also strongly encouraged to establish the DST capacity to test for resistance to bedaquiline and linezolid at baseline (particularly in cases demonstrating fluoroquinolone resistance) and to test samples from patients with no bacteriological conversion after month 4 while on the BPaLM/BPaL regimen.

It is good practice to assess patients for symptoms and signs of liver disease (e.g. fatigue, anorexia, nausea, jaundice, dark urine, liver tenderness and hepatomegaly), peripheral or optic neuropathy and conduct laboratory tests such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase and bilirubin, complete blood count and serum potassium, calcium and magnesium (which should be corrected if abnormal). Treating clinicians are also advised to obtain an ECG before initiation of treatment. A suggested schedule of monitoring is provided in the operational handbook on treatment of DR-TB *(3)*.

The WHO framework for aDSM needs to be applied to patients on any type of MDR-TB regimen, to ensure an acceptable level of monitoring for adverse events and prompt response to such events – alongside monitoring for treatment outcomes, including early monitoring for treatment failure. Additional evidence generated on adverse events will be important to build the evidence base on the safety of the new regimens in varied settings.

Monitoring of changes in dosing and duration of linezolid in particular (when needed) will also be important, to inform the future evidence base on the wider use of the BPaLM/BPaL regimen and the tolerability of linezolid in this regimen.

Section 2. The 9-month all-oral regimen for MDR/RR-TB (NEW)

2.1 Recommendation

NEW RECOMMENDATION

No.	Recommendation
2.1	WHO suggests the use of the 9-month all-oral regimen rather than longer (18-month) regimens in patients with MDR/RR-TB and in whom resistance to fluoroquinolones has been excluded. *(Conditional recommendation, very low certainty of evidence)*

Remarks

1. The 9-month all-oral regimen consists of bedaquiline (used for 6 months), in combination with levofloxacin/moxifloxacin, ethionamide, ethambutol, isoniazid (high-dose), pyrazinamide and clofazimine (for 4 months, with the possibility of extending to 6 months if the patient remains sputum smear positive at the end of 4 months), followed by treatment with levofloxacin/moxifloxacin, clofazimine, ethambutol and pyrazinamide (for 5 months). Ethionamide can be replaced by 2 months of linezolid (600 mg daily).
2. A 9-month regimen with linezolid instead of ethionamide may be used in pregnant women, unlike the regimen with ethionamide.
3. This recommendation applies to:
    a. people with MDR/RR-TB and without resistance to fluoroquinolones;
    b. patients without extensive TB disease[22] and without severe extrapulmonary TB;[23]
    c. patients with less than 1 month exposure to bedaquiline, fluoroquinolones, ethionamide, linezolid and clofazimine; when exposure is greater than 1 month, these patients may still receive this regimen if resistance to the specific medicines with such exposure has been ruled out;
    d. all people regardless of HIV status;
    e. children (and patients in other age groups) who do not have bacteriological confirmation of TB or resistance patterns but who do have a high likelihood of MDR/RR-TB (based on clinical signs and symptoms of TB, in combination with a history of contact with a patient with confirmed MDR/RR-TB).

Rationale

The rationale for this recommendation is based on the evidence and considerations detailed in the next two subsections. The 9-month regimens can be used in patients not eligible for the shorter, 6-month regimens; also, they represent a preferred treatment option over the longer regimens. The

[22] Extensive (or advanced) pulmonary TB disease is defined as the presence of bilateral cavitary disease or extensive parenchymal damage on chest radiography. In children aged below 15 years, advanced disease is usually defined by the presence of cavities or bilateral disease on chest radiography.

[23] Severe extrapulmonary TB is defined as the presence of miliary TB or TB meningitis. In children aged below 15 years, extrapulmonary forms of disease other than lymphadenopathy (peripheral nodes or isolated mediastinal mass without compression) are considered to be severe.

intention to determine a relatively shorter duration of treatment for patients with forms of DR-TB or other eligibility criteria not compatible with the 6-month regimen has driven the assessments presented in this section.

Briefly, two assessments have been performed: first, comparing the outcomes of the 9-month regimen including linezolid for 2 months and the identical regimen that included ethionamide for 4 months; and second, comparing the outcomes of the 9-month regimen including linezolid with the longer regimens that were designed individually but included both bedaquiline and linezolid along with other medicines as recommended by WHO. Data on most of the 9-month regimens were obtained from a programmatic setting in South Africa.

The first assessment showed similar levels of treatment success (64% vs 66%), failure or recurrence (1.1% vs 1.4%), deaths (20% vs 21%), loss to follow-up (15% vs 12%) and amplification of drug resistance (0.6% vs 0%). Adverse events were noted in 5% of participants receiving the 9-month regimen with linezolid; however, no comparisons could be made because no data were available for participants receiving the 9-month regimen with ethionamide. The second assessment of the 9-month regimen compared with longer regimens also showed lower levels of treatment success (64% vs 74%), failure or recurrence (1% vs 3%) or amplification of drug resistance (1% vs 2%); and higher levels of deaths (20% vs 11%) or loss to follow-up (15% vs 12%). Adverse events were noted in 5% of participants receiving the 9-month regimen with linezolid and in participants receiving longer regimens.

Based on a combined review of these two assessments it was considered that the 9-month regimen with linezolid can be recommended as an alternative to the 9-month regimen with ethionamide, and that both regimens can be used in preference to the longer (18-month) regimens in eligible patients. These assessments were performed on the background of the previous assessment during the GDG meeting in 2019 that led to the conditional recommendation for use of the 9-month all-oral bedaquiline-containing regimen *(41)*. The datasets of both 9-month regimens systematically excluded patients with extensive TB disease and severe forms of extrapulmonary TB; therefore, this recommendation is not extended to these groups of patients.

2.2 Summary of evidence

This section provides the PICO questions posed, the data and studies considered to answer the questions, the methods used for analysis and data synthesis, a summary of evidence on desirable and undesirable effects and certainty of evidence, and a summary of other evidence considered during development of the recommendation. Additional detail on the evidence is available in the web annexes containing the GRADE evidence summary tables (**Web Annex 3**) and GRADE evidence-to-decision tables (**Web Annex 4**).

PICO questions

The following PICO question was used for the evidence assessment in 2019 that led to the conditional recommendation for use of the all-oral bedaquiline-containing 9-month regimen.

> *PICO question 2–2019 (MDR/RR-TB, 2019): In MDR/RR-TB patients, does an all-oral treatment regimen lasting 9–12 months and including bedaquiline safely improve outcomes when compared with other regimens conforming to WHO guidelines?*

The following PICO question (split into two sub-PICO questions because of different comparators) guided the analyses and the assessment, and eventually led to a summary recommendation:

PICO question 1–2022 (MDR/RR-TB, 2022): Should a shorter all-oral regimen (less than 12 months) containing at least three Group A medicines[24] be used in patients with MDR/RR-TB and with fluoroquinolone resistance excluded?

Data and studies considered

In 2019, for the WHO guideline update, the South African Department of Health provided WHO with access to programmatic data on injectable-free regimens that had been used in South Africa since 2017, when most eligible patients were enrolled on a shorter regimen, with bedaquiline replacing the injectable *(42)*. In August 2019, WHO issued a public call for IPD on the use of all-oral shorter regimens of 9–12 months *(43)*, but this call yielded no additional evidence on the implementation of such regimens. Consequently, the evidence review on injectable-free regimens in 2019 was based primarily on programmatic data from South Africa, recorded in the Electronic Drug-Resistant Tuberculosis Register (EDRWeb). Secondary comparative analyses were carried out using the IPD, to balance the assumptions and adequacy of the data, and adding to the generalizability of findings – in particular, the applicability to a global population. The IPD used at that time was a global dataset of the records of individual patients who have been treated for MDR/RR-TB; as of November 2019, it contained 13 273 records from 55 studies or centres in 38 countries. The evidence reviews focused on the performance of a standardized shorter regimen in which the injectable agent was replaced by bedaquiline, in combination with levofloxacin (or moxifloxacin), clofazimine, and high-dose isoniazid, ethambutol, pyrazinamide and ethionamide (or prothionamide). Patients on this regimen did not receive any injectable agents, nor were they administered cycloserine, terizidone, *p*-aminosalicylic acid, delamanid or linezolid. According to the clinical guidance issued by the South African Department of Health, at the time of regimen roll-out patients were not enrolled on the all-oral shorter regimen if they had extensive disease, severe extrapulmonary TB, fluoroquinolone resistance, previous exposure to second-line treatment for more than 1 month or genotypic DST showing mutations in both *inh*A and *kat*G genes.

In June 2021, WHO issued a public call *(44)* for IPD on the treatment of DR-TB. The call for individual patients' data on bacteriologically confirmed MDR/RR-TB patients (including MDR/RR-TB, MDR/RR-TB with additional resistance to second-line TB drugs, and patients with pre-XDR-TB or XDR-TB) included the following specifics:

- use of the modified shorter (<12 months) all-oral regimens using at least bedaquiline and linezolid;
- use of the WHO-recommended shorter all-oral bedaquiline-containing regimen (9–11 months) in the following combination: 4 or 6 months of bedaquiline (used for at least 6 months), levofloxacin (or moxifloxacin), clofazimine, pyrazinamide, ethionamide, ethambutol and high-dose isoniazid, followed by 5 months of levofloxacin (or moxifloxacin), clofazimine, pyrazinamide and ethambutol; and
- use of the WHO-recommended longer all-oral treatment regimen containing at least bedaquiline and linezolid.

The South African Department of Health provided WHO with the programmatic data from 2018 to 2019 on the use of a modified 9-month regimen in which ethionamide was replaced by linezolid. Several country programmes that provided WHO with IPD on the use of longer regimens according to WHO recommendations are listed in the Introduction (See *Scope of the 2022 update and available evidence*).

Once again, in 2021, the evidence review was based on programmatic data from South Africa on treatment outcomes of patients treated with the 9-month regimen (with either ethionamide or linezolid), recorded in the EDRWeb. Both datasets from South Africa (2017 and 2018–2019) with the 9-month regimens systematically excluded patients with extensive TB disease (extensive bilateral pulmonary cavitations), severe forms of extrapulmonary TB (meningitis, osteoarticular TB, pericardial effusion and abdominal TB), fluoroquinolone resistance, previous exposure to second-line treatment

[24] The three medicines included in Group A used for classification of second-line medicines are bedaquiline, fluoroquinolones and linezolid.

for more than 1 month or with genotypic DST showing mutations in both *inh*A and *kat*G genes. In addition, comparative analyses were carried out using the 2021 IPD, which was compiled for the review and analyses in preparation for the GDG 2022; this IPD was of individual patients who had been treated for MDR/RR-TB. The evidence review focused on the performance of a standardized shorter regimen in which the injectable agent was replaced by bedaquiline (used for 6 months), in combination with levofloxacin/moxifloxacin, ethionamide, ethambutol, isoniazid (high-dose), pyrazinamide and clofazimine for 4 months (with the possibility of extending to 6 months if the patient remained sputum smear positive at the end of 4 months), followed by 5 months of treatment with levofloxacin/moxifloxacin, clofazimine, ethambutol and pyrazinamide. The comparators used included a nearly identical regimen where ethionamide was replaced by 2 months of linezolid (600 mg once daily) and the set of longer regimens designed based on the 2020 WHO recommendations.

Methods used for analysis and data synthesis

For comparisons between dataset or cohorts, outcomes were presented as unadjusted RRs and aRRs; the latter were calculated using a log-binomial generalized linear regression (binomial error distribution with log link function). Confounders were adjusted for using inverse probability propensity score weighting. No convergence issues with the log-binomial model arose. When outcome rates were close to the boundary (<5 positive or negative cases) aRRs were not calculated and unadjusted RRs alone were presented. For outcomes where the number of outcome events was zero, an unadjusted RD was calculated. For unadjusted RDs or RRs, the score method was used for calculating CIs. These approaches applied where one arm of a randomized trial was being compared with an external population, and in randomized trials in which subgroup analyses were performed (including by fluoroquinolone resistance status). Covariate selection for calculation of propensity scores was based on data availability and clinical knowledge. The covariates considered for inclusion in the propensity scores analysis included age, gender, baseline smear result, HIV status (including antiretroviral treatment status), prior treatment history (including whether previous infection was drug resistant), body mass index, smoking status, diabetes diagnosis, cavitation at baseline, disease site and presence of bilateral disease. For the calculation of aRRs, multiple imputation by chain equations using the "within" propensity score approach was used to account for missing data in potential confounders when the proportion of missing values for a confounder was less than 45%.

Summary of evidence on desirable and undesirable effects and certainty of evidence

PICO 1–2019

The primary analysis performed in 2019 using programmatic data from South Africa indicated that the use of a shorter all-oral bedaquiline-containing regimen in patients with MDR/RR-TB was associated with:

- higher treatment success rates (73% all-oral versus 60% standardized shorter regimen success rates, adjusted odds ratio [aOR] for success versus failure or recurrence: 2.1, 95% CI: 1.1–4.0; aOR success versus death: 1.6, 95% CI: 1.2–2.1; aOR success versus failure, recurrence or death: 1.7, 95% CI: 1.3–2.2; and aOR success versus all unfavourable outcomes: 1.9, 95% CI: 1.6–2.4); and
- lower loss to follow-up than a standardized shorter regimen in which an injectable agent was used (aOR loss to follow-up versus all other outcomes: 0.5, 95% CI: 0.4–0.7).

A similar effect for subgroups of patients with acid-fast bacilli (AFB) smear-positive sputum and PLHIV and HIV-negative patients was observed with the use of the shorter all-oral bedaquiline-containing regimen.

The analysis also indicated that when the shorter all-oral bedaquiline-containing regimen was compared with an injectable-free longer regimen containing bedaquiline, there seemed to be no marked differences in the outcomes observed. However, relatively modest beneficial effects were noted in the direction of the intervention; in particular, success versus failure or recurrence (aOR: 3.9, 95% CI: 1.7–9.1), success versus all unfavourable outcomes (aOR: 1.6, 95% CI: 1.2–2.2) and loss to follow-up (aOR: 0.5, 95% CI: 0.4–0.8), all favouring the use of the all-oral shorter regimen. Further subgroup analysis suggested consistent differences in treatment outcomes, as observed in primary analyses among subgroups, in particular among AFB smear-positive patients and in PLHIV on ART; however, differences in treatment outcomes in all-oral shorter and longer regimens were no longer significant when looking at outcomes for HIV-negative individuals, with the exception of loss to follow-up, which favoured the intervention. The additional comparison also illustrated the effect of a shorter all-oral bedaquiline-containing regimen in comparison with longer regimens without any new drugs. The all-oral shorter regimen performed significantly better across all outcomes and all subgroups in this comparison.

PICO 1–2022

For the assessment performed in preparation for the 2022 GDG, 8 653 records of patients with MDR/RR-TB initiating TB treatment at any time between January and December 2017 were considered, of which the following were included for analyses: 4 244 patients treated with a shorter regimen that included linezolid (used in South Africa in 2019) (intervention), 880 patients who received a shorter all-oral bedaquiline-containing 9-month regimen with ethionamide (used in South Africa in 2017) (comparator), and 850 patients treated with longer regimens that included at least bedaquiline and linezolid.

Sub-PICO 1.1

In sub-PICO 1.1, two observational studies were compared – the 9-month regimen with linezolid (used in South Africa in 2019) (intervention) and the 9-month regimen with ethionamide (used in South Africa in 2017) (comparator). Both datasets were obtained from a programmatic setting in South Africa.

Participants with MDR/RR-TB with fluoroquinolone susceptibility receiving the 9-month regimen with linezolid (*n*=4 244) compared with participants receiving the 9-month regimen with ethionamide (*n*=880) experienced:

- lower levels of treatment success (64% vs 66%); that is, a 4% relative reduction (aRR=0.96, 95% CI: 0.91 to 1.01);
- lower levels of failure and recurrence (1.1% vs 1.4%); that is, a 20% relative reduction (aRR=0.80, 95% CI: 0.42 to 1.53);
- higher levels of deaths (20% vs 21%); that is, a 3% relative increase (aRR=1.03, 95% CI: 0.89 to 1.20);
- higher levels of loss to follow-up (15% vs 12%); that is, a 19% relative increase (aRR=1.19, 95% CI: 0.98 to 1.45); and
- higher levels of amplification of drug resistance (0.6% vs 0%); that is, a 1% absolute increase (RD=0.01, 95% CI: 0.00 to 0.01).

Adverse events were noted in 5% of participants receiving the 9-month regimen with linezolid but no comparisons could be made because no data were available for participants receiving the 9-month regimen with ethionamide.

The GDG judged the benefits of the 9-month regimen with linezolid to be small and the undesirable effects to be moderate compared with the 9-month regimen with ethionamide. The certainty of evidence was judged to be very low. Based on this, the GDG judged that the balance of health effects does not favour either the 9-month regimen with linezolid or the 9-month regimen with ethionamide.

Conclusion

The use of either the 9-month regimen with linezolid or the 9-month regimen with ethionamide is suggested in people with pulmonary MDR/RR-TB without fluoroquinolone resistance (conditional recommendation, very low certainty of evidence).

Sub-PICO 1.2

In sub-PICO 1.2, two observational datasets were compared – the 9-month regimen with linezolid (used in South Africa in 2019) (intervention) and the all-oral longer regimens containing bedaquiline from the 2021 IPD dataset.

Participants with MDR/RR-TB with fluoroquinolone susceptibility receiving the 9-month regimen with linezolid (*n*=4 244) compared with participants receiving longer regimens for MDR/RR-TB (*n*=850) experienced:

- lower levels of treatment success (64% vs 74%); that is, a 10% relative reduction (aRR=0.90, 95% CI: 0.83 to 0.98);
- lower levels of failure and recurrence (1.1% vs 3.4%); that is, a 71% relative reduction (aRR=0.29, 95% CI: 0.14 to 0.58);
- higher levels of deaths (20% vs 11%); that is, a 38% relative increase (aRR=1.38, 95% CI: 1.00 to 1.91);
- higher levels of loss to follow-up (15% vs 12%); that is, a 33% relative increase (aRR=1.33, 95% CI: 0.97 to 1.81);
- similar levels of adverse events (5.0% vs 4.7%), (aRR=1.00, 95% CI: 0.59 to 1.69); and
- lower levels of amplification of drug resistance (0.6% vs 1.4%); that is, a 73% relative reduction (aRR=0.27, 95% CI: 0.12 to 0.61).

The GDG judged both the benefits of the 9-month regimen with linezolid and the undesirable effects to be moderate compared with the longer regimens. The certainty of evidence was judged to be very low. Based on this, the GDG judged that the balance of health effects did not favour either the 9-month regimen with linezolid or the longer regimens. The panel judged that although the balance of effects did not favour either the intervention or the comparator, several other criteria in the GRADE evidence-to-decision tables (e.g. resources, acceptability, equity and feasibility) favoured the 9-month regimen.

Conclusion

The use of either the 9-month regimen with linezolid or the longer (18-month) regimens is suggested in people with pulmonary MDR/RR-TB without fluoroquinolone resistance (conditional recommendation, very low certainty of evidence).

Summary of other evidence

During assessment of sub-PICO 1.1, the panel noted that the cost of component medicines is likely to be similar because both regimens are of the same duration and use the same component medicines except for one – linezolid instead of ethionamide. The duration of linezolid use is 2 months compared with 4 months for ethionamide. Based on GDF prices *(45)* the cost difference was negligible (2 months of linezolid at 600 mg/day US$ 21, and 4 months of ethionamide at 450 mg/day US$ 32).

The health care costs are also likely to be similar because the two regimens are of the same duration and have the same component medicines, except for one – linezolid instead of ethionamide.

The panel also assumed no difference in DST needs. Both regimens are indicated for patients with MDR/RR-TB and without fluoroquinolone resistance. These patients are usually tested for rifampicin

and fluoroquinolone resistance – rapid DSTs for both of these medicines are available. It might also be useful to perform genotypic DST because mutations in the *inh*A gene also confer resistance to ethionamide.

2.3 Evidence to recommendations: considerations

In 2022, new evidence from programmatic implementation in South Africa was made available to WHO where the regimen was modified to include 2 months of linezolid (600 mg) instead of 4 months of ethionamide.

Based on an assessment of the certainty of the evidence, carried out using predefined criteria and documented in the GRADEpro software, the certainty of the evidence was rated as very low for both comparisons.

Table 2.1 lists the comparisons and decisions on each of the sub-PICO questions that were assessed by the GDG to conclude with the summary recommendation (Recommendation 2.1). The main assessment that defined the overall decision was based on sub-PICO 1.1. The background for this decision was provided by the previous review and recommendation for the use of the 9-month regimen with ethionamide agreed during the GDG meeting in November 2019 and reflected in the recommendations published in the 2020 DR-TB treatment guidelines update *(41)*.

Table 2.1. PICO questions and decisions of the GDG panel

#	PICO	Population	Intervention	Comparator [data source]	Comparison#	Decision
2–2019	In MDR/RR-TB patients, does an all-oral treatment regimen lasting 9–12 months and including bedaquiline safely improve outcomes when compared with other regimens conforming to WHO guidelines?	MDR/RR-TB	9-month regimen with ethionamide	9-month regimen with injectables; or longer regimens	1	Conditional for intervention
1–2022	Should a shorter all-oral regimen (less than 12 months) containing at least three Group A medicines be used in patients with MDR/RR-TB and fluoroquinolone resistance excluded?	MDR/RR-TB	9-month regimen with linezolid	9-month regimen with ethionamide	1.1	Conditional for either intervention or comparator
				Longer regimens	1.2	Conditional for either intervention or comparator

GDG: Guideline Development Group; MDR/RR-TB: multidrug-resistant or rifampicin-resistant TB; PICO: population, intervention, comparator and outcome; TB: tuberculosis; WHO: World Health Organization.

Sub-PICO 1.1

The GDG acknowledged that, during the analysis, the intervention and comparator groups were made as comparable as possible. However, the GDG considered possible unmeasured confounding due to a lack of systematic collection of information on comorbidities and radiological findings through the EDRWeb system, as well as methodological challenges (e.g. a potential selection bias). Apart from the selection criteria listed, the risk of major selection bias was considered to be low, given that this intervention represented a complete and comprehensive switch in the countrywide programmatic approach.

Regarding generalizability, the GDG deliberated whether the genetic diversity of *M. tuberculosis* strains in South Africa was comparable to strains present in other settings; the group concluded that strains found in other settings were adequately represented in the country. The group also considered potential interactions in relation to HIV status and the effect of ART, but this was not considered a major factor given that treatment outcomes were similar in PLHIV and HIV-negative people. The GDG agreed that results of the STREAM Stage 2 trial – a large-scale, multicountry Phase 3 trial examining a shorter all-oral bedaquiline-containing regimen – will provide additional important insight into the efficacy and safety of this regimen, and may increase the certainty of the evidence.

A clear limitation emphasized by the GDG was the lack of data on adverse events in the EDRWeb. No direct comparative evidence was available on adverse events because the data on such events were not systematically collected for the 9-month regimen with ethionamide. The rate of Grade 3–5 adverse events was 5% for the 9-month regimen with linezolid. The panel nevertheless considered the potential adverse events of both ethionamide and linezolid in balancing the benefits and harms (**Table 2.2**).

Table 2.2. Summary of adverse events associated with linezolid and ethionamide

Linezolid adverse events	Ethionamide adverse events
• Myelosuppression (anaemia, decreased level of white blood cells or decreased level of platelets) • Peripheral or optic neuropathy – these conditions may be irreversible, and linezolid should be stopped if they develop • Lactic acidosis – patients who develop recurrent nausea or vomiting, unexplained acidosis or a low bicarbonate level while receiving linezolid should receive immediate medical evaluation, including a lactic acid blood test • Diarrhoea and nausea	• Gastrointestinal upset and anorexia (sometimes intolerable) – symptoms are moderated by food or by taking at bedtime • Hepatotoxicity • Endocrine effects (e.g. gynaecomastia, hair loss, acne, impotence, menstrual irregularity and reversible hypothyroidism) • Neurotoxicity – patients taking ethionamide should take high doses of vitamin B6

The panel also considered the duration and pill burden with the intervention and comparator regimens. Both regimens have the same duration, so neither offers an advantage of shorter treatment, although the duration of the linezolid regimen is shorter than that of ethionamide. The pill burden is likely to be slightly lower with the intervention because linezolid is prescribed for 2 months in the 9-month regimen with linezolid and ethionamide for 4 months in the 9-month regimen with ethionamide.

Considering this evidence, the panel judged that the 9-month regimen with linezolid may have small desirable effects and noted the very low certainty of the evidence. Certainty of the evidence was rated "very low" for all outcomes on account of potential misclassification bias and confounding bias (downgraded 1 level), and serious indirectness (downgraded 1 level). The overall certainty is generally based on the lowest certainty for the agreed critical outcomes; thus, it was judged to be very low. The

panel noted that the evidence on both the intervention and on the comparator regimen was obtained from programmatic data from South Africa such that, overall, the population and health care context were comparable. However, the panel stressed that important differences exist between the two cohorts or datasets that were compared, making it difficult to draw conclusions with full confidence.

The panel judged that there was probably no important uncertainty or variability in how much people value the main outcomes. The panel used available data on cost of component medicines combined with professional judgement to estimate the cost of the 9-month regimen with linezolid compared with the 9-month regimen with ethionamide among patients with MDR/RR-TB, susceptible to fluoroquinolones. The panel suggested that the cost would be expected to be very similar; that is, for there to be negligible costs or savings. The panel also noted that no data were available on the cost of managing potential long-term consequences of neurotoxicity that can be caused by the use of linezolid, and that the risk is greater if linezolid is used for longer periods. The panel has also noted that health care and patient costs are likely to be similar for regimens when used in a similar group of patients and for the same duration.

The GDG attempted to discuss cost–effectiveness of the two regimens; however, no evidence was available, the two regimens are identical in duration and they only differ in one component drug, which would not change the overall cost of the regimen in any significant way. The similarity of the two regimens also prevented a substantial discussion on the equity. The panel considered patients and health care providers as key stakeholders. The panel considered the following aspects as critical with regard to acceptability: regimen duration, drug-safety monitoring needs (relating both to the necessary travel, loss of income and general disruption of the life of patients, and to workload for the health care system) and DST needs. The panel judged that there were probably no differences in acceptability between the 9-month regimen with linezolid and the 9-month regimen with ethionamide, given the overall similarity of the regimens, and that the 9-month regimen with linezolid would probably be acceptable. The panel considered the following aspects to affect feasibility (i.e. to be potential barriers to implementation): requirements for drug-safety monitoring and for DST. The 9-month regimen with linezolid would require monitoring of toxicity (e.g. anaemia) and DST.

The panel judged that the balance of desirable and undesirable consequences favours neither the 9-month regimen with linezolid nor the 9-month regimen with ethionamide in this population. Specifically, the panel felt that there is a fine balance between the two options in terms of benefits and harms that is uncertain given the overall very low certainty in the evidence (due to potential misclassification bias, confounding bias and serious indirectness). The panel judged that for most other evidence-to-decision criteria (e.g. resources, acceptability and feasibility) there was unlikely to be a large difference between the 9-month regimen with linezolid and the 9-month regimen with ethionamide because the only difference between the two regimens is the replacement of ethionamide with linezolid. Overall, the panel judged that either regimen could be used and that the flexibility of using either linezolid or ethionamide was helpful to optimize patient care. These considerations also guided the agreement of the panel on the strength of the recommendation being conditional.

Sub-PICO 1.2

The GDG acknowledged that, during the analysis, the intervention and comparator groups were made as comparable as possible. The panel noted that the evidence on the 9-month regimen was obtained from programmatic data from South Africa, whereas the evidence on the longer regimen represented only subsets of patients from the countries and researchers that submitted data. The panel also noted substantial inconsistency between cohorts in the comparator group (on the longer regimens). Overall, there was concern that the selective nature of the data on the longer regimens may have biased the comparison in favour of the longer regimen. As a result, there were serious concerns about the comparability of the data, making it difficult to draw conclusions with confidence. The panel also considered the duration and overall pill burden with the intervention and comparator regimens, which are both lower in the 9-month regimen and thus represent a benefit of the intervention.

Considering this evidence and the totality of observed effects of the 9-month regimen with linezolid on the outcomes, the panel judged that the 9-month regimen with linezolid may have moderate desirable effects and that it may also have moderate undesirable effects.

Certainty in the estimates was rated "very low" for all outcomes owing to very serious risk of bias (potential misclassification bias and confounding bias), inconsistency (inconsistency in the effect estimates among 14 comparator cohorts) and indirectness (with data for the intervention regimen being from a single country). The overall certainty is generally based on the lowest certainty for the agreed critical outcomes and thus was judged to be very low.

The panel noted that the costs for people with MDR/RR-TB receiving the 9-month regimen with linezolid are expected to be lower than those for longer regimens (18 months or longer) because costs for drugs, care and monitoring are expected to be lower.

The panel considered the ability to decentralize treatment (to enable access for remote, underserviced settings and disadvantaged populations) as affecting equity. Despite not being able to identify relevant research evidence, the panel used their collective experience to judge that there would probably be advantages associated with the use of the 9-month regimen owing to its reduced complexity and shorter duration. The panel judged that use of the 9-month regimen with linezolid would probably increase equity.

The panel considered patients and health care providers as key stakeholders and the following aspects as critical with regard to acceptability: regimen duration and drug safety, monitoring needs (relating both to the necessary travel, loss of income and general disruption of the life of patients, and to workload for the health care system) and needs for DST. The panel judged that the 9-month regimen with linezolid would probably be acceptable to key stakeholders.

The balance of desirable and undesirable consequences was judged to not favour either the use of the 9-month regimen or the longer, 18-month regimens in this population. Specifically, the panel felt that there is a fine balance between the two options in terms of benefits and harms that is uncertain given the overall very low certainty in the evidence. The panel judged that although the balance of effects did not favour either the intervention or the comparator, several other evidence-to-decision table criteria (e.g. resources, acceptability, equity and feasibility) favoured the 9-month regimen.

Overall, the panel judged that either regimen could be used in the eligible patient group presented in the analysis; they noted the more limited eligibility for the 9-month regimen and acknowledged that the applicability of the longer, individualized regimens is more flexible and significantly broader, including many patient groups that are not eligible for the shorter regimen. These considerations have also guided the agreement of the panel on the conditionality of this recommendation.

2.4 Subgroup considerations

Based on research evidence and expert experience, the panel identified subpopulations of people who might be affected differently than most by this recommendation; these subpopulations were PLHIV, children, pregnant women, breastfeeding women, patients with extrapulmonary TB and patients with extensive TB disease. The recent new recommendation for use of bedaquiline in children with MDR/RR-TB aged below 6 years was considered *(31)*. The panel noted specific considerations for the subpopulations listed below.

People living with HIV

The data evaluated corresponded to a setting with a high prevalence of HIV; of particular significance was that most PLHIV (>90%) who started the 9-month regimens were receiving ART. In view of the treatment outcomes described in the analysis, there were no grounds to believe that the regimen would perform any differently in PLHIV. It is necessary to consider significant clinical interactions that

may increase bedaquiline exposure or that of other agents with potential for cardiotoxicity when these are co-administered with antiretroviral drugs. However, because the data evaluated did not include information on changes to the regimen as a result of management of adverse drug reactions, or complications from drug–drug interactions, the GDG reiterated that it is worth paying attention to any potential drug–drug interactions or overlapping drug toxicities that may not have been captured. For example, bedaquiline concentrations can be reduced by efavirenz (these drugs should not be co-administered) or increased by boosted protease inhibitors (resulting in a need for greater vigilance in monitoring for drug-related QT effects) *(46–48)*. Neuropathy, liver enzyme elevations and CNS side-effects can be attributed to HIV or TB drugs or their interactions *(49)*.

Children

The datasets included only small numbers of people aged below 15 years (*n*=69), and thus did not allow for reliable comparisons in both datasets from South Africa (*n*=69 and *n*=7) and in the 2021 IPD (*n*=7). However, analysis in the subgroup aged below 15 years showed a relative increase in treatment success of 42% (aRR=1.42, 95% CI: 0.7 to 2.89) in sub-PICO 1.1 and a 5% relative reduction (RR=0.95, 95% CI: 0.78 to 1.15) in sub-PICO 1.2. Although a small number of participants were aged between 10 and 15 years (19/50, 38% in the intervention group, and 75/162, 46% in the comparator group), extrapolation of the findings to children was deemed reasonable for efficacy because components of the regimen had been used safely in children based on other available data regarding linezolid use in children. This extrapolation was considered applicable to children of all ages, taking into account the recommendation for use of bedaquiline in children aged below 6 years *(31)*.

Pregnant and lactating women

In the research studies analysed, pregnant women were not identified, and subgroup data were unavailable. Ethionamide is usually contraindicated in pregnancy (because animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans), and this is the main reason that the 9-month regimen has not been recommended for this subgroup in the past. There is experience in using linezolid during pregnancy *(50, 51)*. For pregnant and lactating women, it is therefore recommended to use the regimen with linezolid instead of ethionamide.

Extrapulmonary TB

A subgroup of people with extrapulmonary TB were included in the research studies (81 in the regimen containing linezolid and 23 in the regimen with ethionamide). In view of the unavailability of evidence on surrogates for severity or extent of disease, the use of this regimen in patients with severe forms of extrapulmonary TB is not recommended.

2.5 Implementation considerations

Patient selection and decisions to start the 9-month regimens

Patient selection and decisions to start the 9-month regimens in newly diagnosed patients should be made through an informed decision-making process that includes patient preference and clinical judgement, and DST results available before the start of treatment.

These regimens can be a preferred option over the longer regimens and can be used in those who are not eligible for the shorter BPaLM/BPaL regimens. Patients with confirmed MDR/RR-TB and in whom resistance to fluoroquinolones has been ruled out are expected to benefit the most from 9-month regimens. Proper patient selection would not only lead to improved treatment outcomes but would also contribute to protecting against the development of bedaquiline resistance. In this respect, the

regimen is to be implemented only in settings where routine DST for rifampicin and fluoroquinolones can be guaranteed.

Patients should be informed about the advantages and possible disadvantages so that they can make an informed decision on the regimen of choice. Previous exposure of less than 1 month duration to the second-line medicines used in the regimen needs to be ascertained; it can then be considered along with any additional DST results available. Based on the available evidence, this regimen can be used in patients with confirmed MDR/RR-TB (with at least confirmed resistance to rifampicin) in whom resistance to fluoroquinolones has been ruled out, in the following situations: no exposure to previous treatment with second-line medicines in the regimen for more than 1 month (unless susceptibility to these medicines is confirmed); or no extensive TB disease and no severe extrapulmonary TB.

Drug susceptibility testing

DST for bedaquiline and linezolid is an important implementation consideration that will need to be enhanced in many countries, given the increasing use of these medicines in all regimens for MDR/RR-TB and the possible further inclusion of new medicines in MDR-TB treatment regimens. The implementation of these recommendations must be accompanied by continued efforts to increase access to DST for all medicines for which reliable methods are currently available, and for the development and roll-out of DST methods for newer medicines. **Access to WHO-recommended rapid DST is essential, especially for detecting resistance to rifampicin and fluoroquinolones, before starting the 9-month regimens. Baseline DST will confirm eligibility for different regimen options; therefore, the establishment and strengthening of DST services is a vital consideration for implementation**. The DST methods for identifying resistance to bedaquiline and linezolid have been developed on available phenotypic platforms and need to be implemented in all settings where these medicines are being used. Resistance to other anti-TB drugs should be monitored in accordance with WHO recommendations.

One of the exclusion criteria for all shorter regimens in the datasets from South Africa was mutations in both *inh*A promoter and *kat*G regions, confirmed using a line probe assay (LPA). This means that patients with only *inh*A or only *kat*G mutations were included. A first-line LPA (MTBDRplus) and Xpert MTB/XDR cartridge can determine mutations in the *inh*A promoter or *kat*G regions; both mutations confer resistance to isoniazid, with the resistance being low level when *inh*A mutations alone are present, or high level with *kat*G gene mutations alone or *inh*A promoter and *kat*G gene mutations combined. Mutations at the *inh*A promoter are also associated with resistance to ethionamide and prothionamide. The presence of mutations in both the *inh*A promoter and *kat*G suggests that isoniazid at high dose and thioamides are not effective, and that the 9-month regimen may not therefore be used. In the absence of information on mutation patterns for an individual patient, the decision can be informed by knowledge of the frequency of the concurrent occurrence of both mutations, obtained from drug-resistance surveillance *(52)*. Phenotypic DST for some medicines included in the regimen (e.g. ethambutol and ethionamide) is not considered reliable and reproducible; therefore, this testing should be employed with caution to inform the use of this regimen.[25]

Currently, there is limited capacity globally to carry out DST for bedaquiline; however, laboratory capacity should be strengthened in this area as new medicines and regimens begin to be used more widely. National and reference laboratories will need to have the relevant reagents available to enable DST to be carried out and will need data on the MIC distribution of all *M. tuberculosis* lineages that are circulating globally. The WHO TB SRL Network is available to support national TB reference laboratories in performing quality-assured DST. A WHO technical consultation in 2017 established critical concentrations for susceptibility testing for the fluoroquinolones, bedaquiline, delamanid, clofazimine and linezolid *(35)*.

[25] See the list of high-confidence resistance-conferring mutations in the WHO guide on the use of next-generation sequencing technologies, WHO (2018) *(53)*.

Selection of fluoroquinolones

Selection of fluoroquinolones may take into account the evidence from South Africa available for the review – 83% of patients analysed using the 2017 dataset received levofloxacin and the rest received moxifloxacin at standard dose (400 mg daily). Both levofloxacin and moxifloxacin have shown similar efficacy for treating DR-TB. The choice between levofloxacin and moxifloxacin was guided by the potential risk of cumulative cardiotoxicity, using moxifloxacin in a shorter regimen with injectables and levofloxacin in an all-oral shorter regimen. Levofloxacin is often preferred because of moxifloxacin's slightly higher potential for cardiotoxicity; however, levofloxacin has been associated with musculoskeletal disorders in paediatric populations. Therefore, irrespective of the choice of fluoroquinolone, **NTPs need to implement aDSM in all patients enrolled on treatment of DR-TB** *(39, 54)*.

Assessment of TB disease

To determine regimen options, it is important to know the extent of TB disease, in addition to the DST results and other considerations mentioned above. Extensive TB disease is defined in this document as the presence of bilateral cavitary disease or extensive parenchymal damage on chest radiography. In children aged below 15 years, advanced disease is usually defined by the presence of cavities or bilateral disease on chest radiography. **This highlights the importance of chest radiography as part of the diagnostic and clinical management work-up for patients.**

Regimen duration

The regimen comprises an intensive phase of 4 months that may be extended to 6 months when no bacteriological conversion is seen at the end of the fourth month of treatment, and a continuation phase of 5 months; hence, if extended, the regimens may last 11 months. In the dataset reviewed, the duration of bedaquiline and linezolid was restricted to 6 and 2 months, respectively.

Patient-centred approach

Efforts are required to provide patient support to enable full adherence to treatment.

2.6 Monitoring and evaluation

Patients who receive a shorter MDR-TB treatment regimen need to be monitored during treatment using schedules of relevant clinical and laboratory testing, which have been successfully applied in previous studies of shorter regimens under field conditions and in the programmatic setting in South Africa.

The GDG emphasized the need to strengthen and increase access to DST, and the need to monitor and undertake surveillance for emerging drug resistance, including for bedaquiline and for all second-line medicines in the shorter regimen for which reliable DST is available.

The schedule of bacteriological monitoring in South Africa included both smear and culture, carried out monthly. Therefore, the response to treatment should be monitored by using monthly sputum smear microscopy, and culture (ideally at the same frequency). This is similar to the schedule of bacteriological monitoring recommended for the longer regimens (**Section 3**). If feasible, it is also important to follow up patients 12 months after the completion of treatment, for possible relapse, including with sputum culture and smear.

Based on guidance in current literature and collective experience, the panel advised the following with regard to monitoring and evaluation of the safety and effectiveness of the 9-month regimens:

- the implementation of both regimens requires the use of routine DST, not only for patient selection but also to monitor the acquisition of resistance (collection of strains for sequencing should be considered);
- although the data assessed did not unearth any major signals of risk, aDSM systems must be functional to conduct rigorous active monitoring of adverse events and to detect, manage and report suspected or confirmed drug toxicities in a timely manner;
- programmes need to have access to reliable DST for bedaquiline and linezolid when no bacteriological conversion is seen at the end of the fourth month of treatment and following the 2 months of prolongation – in an ideal situation, the DST for all second-line medicines in these regimens would be available; and
- wider applicability of the 9-month regimens highlights the importance of paediatric formulations. Programmes and their partners need to address the sustained availability of modern paediatric formulations to ensure smooth implementation in this subgroup of patients.

Section 3. Longer regimens for MDR/RR-TB

Recommendations

No.	Recommendation
3.1	In multidrug- or rifampicin-resistant tuberculosis (MDR/RR-TB) patients on longer regimens, all three Group A agents and at least one Group B agent should be included to ensure that treatment starts with at least four TB agents likely to be effective, and that at least three agents are included for the rest of the treatment if bedaquiline is stopped. If only one or two Group A agents are used, both Group B agents are to be included. If the regimen cannot be composed with agents from Groups A and B alone, Group C agents are added to complete it. *(Conditional recommendation, very low certainty of evidence)*
3.2	**Kanamycin and capreomycin** are not to be included in the treatment of MDR/RR-TB patients on longer regimens. *(Conditional recommendation, very low certainty of evidence)*
3.3	**Levofloxacin or moxifloxacin** should be included in the treatment of MDR/RR-TB patients on longer regimens. *(Strong recommendation, moderate certainty of evidence)*
3.4	**Bedaquiline** should be included in longer multidrug-resistant TB (MDR-TB) regimens for patients aged 18 years or more. *(Strong recommendation, moderate certainty of evidence)* **Bedaquiline** may also be included in longer MDR-TB regimens for patients aged 6–17 years. *(Conditional recommendation, very low certainty of evidence)* In children with MDR/RR-TB aged below 6 years, an all-oral treatment regimen containing **bedaquiline** may be used. *(Conditional recommendation, very low certainty of evidence)*
3.5	**Linezolid** should be included in the treatment of MDR/RR-TB patients on longer regimens. *(Strong recommendation, moderate certainty of evidence)*
3.6	**Clofazimine and cycloserine or terizidone** may be included in the treatment of MDR/RR-TB patients on longer regimens. *(Conditional recommendation, very low certainty of evidence)*

No.	Recommendation
3.7	**Ethambutol** may be included in the treatment of MDR/RR-TB patients on longer regimens. *(Conditional recommendation, very low certainty of evidence)*
3.8	**Delamanid** may be included in the treatment of MDR/RR-TB patients aged 3 years or more on longer regimens. *(Conditional recommendation, moderate certainty of evidence)* In children with MDR/RR-TB aged below 3 years **delamanid** may be used as part of longer regimens. *(Conditional recommendation, very low certainty of evidence)*
3.9	**Pyrazinamide** may be included in the treatment of MDR/RR-TB patients on longer regimens. *(Conditional recommendation, very low certainty of evidence)*
3.10	**Imipenem–cilastatin or meropenem** may be included in the treatment of MDR/RR-TB patients on longer regimens. *(Conditional recommendation, very low certainty of evidence)*[26]
3.11	**Amikacin** may be included in the treatment of MDR/RR-TB patients aged 18 years or more on longer regimens when susceptibility has been demonstrated and adequate measures to monitor for adverse reactions can be ensured. If amikacin is not available, streptomycin may replace amikacin under the same conditions. *(Conditional recommendation, very low certainty of evidence)*
3.12	**Ethionamide or prothionamide** may be included in the treatment of MDR/RR-TB patients on longer regimens only if bedaquiline, linezolid, clofazimine or delamanid are not used, or if better options to compose a regimen are not possible. *(Conditional recommendation against use, very low certainty of evidence)*
3.13	***P*-aminosalicylic acid** may be included in the treatment of MDR/RR-TB patients on longer regimens only if bedaquiline, linezolid, clofazimine or delamanid are not used, or if better options to compose a regimen are not possible. *(Conditional recommendation against use, very low certainty of evidence)*
3.14	**Clavulanic acid** should not be included in the treatment of MDR/RR-TB patients on longer regimens. *(Strong recommendation against use, low certainty of evidence)*[26]
3.15	In MDR/RR-TB patients on longer regimens, a **total treatment duration of 18–20 months** is suggested for most patients; the duration may be modified according to the patient's response to therapy. *(Conditional recommendation, very low certainty of evidence)*
3.16	In MDR/RR-TB patients on longer regimens, a **treatment duration of 15–17 months after culture conversion** is suggested for most patients; the duration may be modified according to the patient's response to therapy. *(Conditional recommendation, very low certainty of evidence)*
3.17	In MDR/RR-TB patients on longer regimens containing amikacin or streptomycin, **an intensive phase of 6–7 months** is suggested for most patients; the duration may be modified according to the patient's response to therapy. *(Conditional recommendation, very low certainty of evidence)*

[26] Imipenem–cilastatin and meropenem are administered with clavulanic acid, which is available only in formulations combined with amoxicillin. Amoxicillin–clavulanic acid is not counted as an additional effective TB agent, and should not be used without imipenem–cilastatin or meropenem.

Table 3.1 gives details of the grouping of medicines recommended for use in longer MDR-TB regimens; the groups are summarized here for clarity:

- Group A = levofloxacin or moxifloxacin, bedaquiline and linezolid;
- Group B = clofazimine, and cycloserine or terizidone; and
- Group C = ethambutol, delamanid, pyrazinamide, imipenem–cilastatin or meropenem, amikacin (or streptomycin), ethionamide or prothionamide, and *p*-aminosalicylic acid.

3.2 Justification and evidence

This section refers to recommendations on MDR/RR-TB treatment regimens that are of longer duration than the regimens described in **Sections 1** and **2**.

PICO questions

The recommendations in this section address PICO questions formulated in 2018 and 2019. The questions formulated in 2018 were as follows:

> ***PICO question 3–2018*** *(MDR/RR-TB, 2018): In patients with MDR/RR-TB, which individual agents are more likely to improve outcomes when forming part of a longer regimen conforming to WHO guidelines?*[27]
>
> ***PICO question 4–2018*** *(MDR/RR-TB, 2018): In patients with MDR/RR-TB on longer regimens composed in accordance with WHO guidelines, are outcomes safely improved with fewer or more than five effective medicines in the intensive phase?*
>
> ***PICO question 5–2018*** *(MDR/RR-TB, 2018): In patients with MDR/RR-TB on longer regimens composed in accordance with WHO guidelines, are outcomes safely improved with an intensive phase shorter or longer than 8 months?*
>
> ***PICO question 6–2018*** *(MDR/RR-TB, 2018): In patients with MDR/RR-TB on longer regimens composed in accordance with WHO guidelines, are outcomes safely improved with a total duration shorter or longer than 20 months?*
>
> ***PICO question 7–2018*** *(MDR/RR-TB, 2018): In patients with MDR/RR-TB on longer regimens composed in accordance with WHO guidelines, what is the minimum duration of treatment after culture conversion that is most likely to improve outcomes?*

The two relevant PICO questions considered by the GDG for the 2020 update were as follows:

> ***PICO question 8–2019*** *(MDR/RR-TB, 2019): In MDR/RR-TB patients, does a treatment regimen containing bedaquiline for more than 6 months safely improve outcomes when compared with bedaquiline for up to 6 months as part of longer regimens otherwise conforming to WHO guidelines?*
>
> ***PICO question 9–2019*** *(MDR/RR-TB, 2019): In MDR/RR-TB patients, does concurrent use of bedaquiline and delamanid safely improve outcomes when compared with other treatment regimen options otherwise conforming to WHO guidelines?*

Two additional PICO questions were reviewed in 2021 as part of the GDG formed to update childhood TB guidelines *(31)*:

PICO question 1–2021 *(Childhood TB, 2021):* In MDR/RR-TB patients aged below 6 years, should an all-oral treatment regimen containing bedaquiline versus other regimens conforming to WHO guidelines without bedaquiline be used?

[27] Given that few trials or other studies have made head-to-head comparisons of MDR-TB medicines at different dosage regimens, it is not expected that guidance on dosage adjustment will be affected by the findings of the systematic review.

PICO question 2–2021 *(Childhood TB, 2021):* In MDR/RR-TB patients aged below 3 years, should an all-oral treatment regimen containing delamanid versus other regimens conforming to WHO guidelines without delamanid be used?

Recommendations for the design of longer MDR-TB regimens have been issued by WHO for several years and have been implemented in many countries worldwide *(1, 8, 11, 12)*. The recommendations in this section cover all forms of MDR/RR-TB; they include treatment of patients with strains resistant to rifampicin and susceptible to isoniazid (i.e. RR-TB), or with additional resistance to isoniazid (i.e. MDR-TB), or with resistance to other medicines (i.e. pre-XDR or XDR-TB). All patients with TB – children or adults – diagnosed with strains shown to be resistant to rifampicin can be placed on an MDR/RR-TB treatment regimen *(12)*.

The likelihood of treatment success in MDR/RR-TB patients on longer regimens depends on factors related to the patient and strain of TB (e.g. severity of disease, resistance patterns and comorbidities), and access to health care (e.g. regimens with sufficient effective agents, medications of good quality, management of adverse events and patient support). Longer regimens with sufficient effective agents are known to increase the likelihood of cure and lower the risk of death in adults and children *(55–58)*. The composition of longer regimens is governed by the selection of individual medicines considered to be effective, and by a need to combine sufficient medicines to maximize the likelihood of relapse-free cure without increasing toxicity. Regimens may be of standardized (fixed) composition or may be individualized to the patient's needs. Longer regimens usually last 18–20 months or more; this document provides recommendations on the duration of such regimens, updated since publication of the 2011 WHO guidelines *(8)*. In summary, in 2018, a total treatment duration of 18–20 months and a treatment duration of 15–17 months after culture conversion were suggested for most patients, with the duration being modified according to the patient's response to therapy.

Evidence base and analyses

Ahead of the GDG discussion in 2018, WHO made a public call for individual MDR/RR-TB patient data, complete with results of treatment *(59)*. IPD meta-analysis in adults and children treated with longer MDR/RR-TB regimens allows the study of useful correlates of outcome, including the regimen composition *(55–57)*. The evidence base for the effectiveness of many of the medicines used in MDR/RR-TB regimens relies on the 2018 IPD meta-analysis. In turn, this IPD meta-analysis relies heavily on observational studies, only a few of which have employed randomized controlled designs *(18)*; hence, the overall certainty of evidence is often graded as low or very low. The sources of data used by the GDGs to address the PICO questions in this section are summarized below.

PICO question 3–2018 (MDR/RR-TB, 2018) (choice of individual medicines)

First, to analyse treatment success, treatment failure, relapse and death for the individual medicines in longer regimens, the 2018 IPD meta-analysis was used, with 13 104 records from 53 studies in 40 countries. The 2018 IPD contained datasets from preceding years and from several countries, including a large dataset from South Africa with many patients treated with bedaquiline-containing regimens. Second, to analyse adverse events resulting in permanent discontinuation of individual medicines in longer regimens, a subset of 5 450 records from 17 studies in the 2018 IPD was used, supplemented with additional information from 10 other studies that only reported adverse events for either bedaquiline (n=130), linezolid (n=508) or carbapenems (n=139).

In addition to these data, the GDG 2018 assessed unpublished results from the Phase 3 Trial 213 of delamanid *(60, 61)* and safety and pharmacological exposure data from unpublished paediatric studies of bedaquiline (Phase 2 TMC207-C211 and Phase 1–2 IMPAACT P1108) and delamanid (Phase 1 242–12–245, Phase 1 242–12–232, Phase 2 242–07–204 and Phase 2 242–12–233). The GDG 2018 also searched the literature for studies reporting outcomes of patients treated with agents other than those included in the 2016 guidelines (e.g. perchlozone, interferon gamma and sutezolid).

PICO question 4–2018 (MDR/RR-TB, 2018) (number of agents likely to be effective)

To analyse treatment success, treatment failure, relapse and death for the optimal number of medicines to be included in longer regimens, the data were derived from a subset of 8 957 patients in 47 studies included in the IPD used for PICO question 2–2018 (MDR/RR-TB, 2018) above. Of these, 3 570 patients in 16 studies had information on the start and end dates for individual medicines in which DST was reported, and 5 387 patients in 31 studies had information on individual medicines used in both the intensive and continuation phases of treatment, as well as DST results. This question focused on the number of agents in the intensive phase; hence, patients who did not receive an injectable agent or in whom an initial intensive phase was not defined were excluded (*n*=476). Patients who were designated "cured" or "treatment completed" but received less than 18 months of treatment – the minimum duration for longer regimens recommended by WHO in the past – were also excluded (*n*=346). In cases where DST results were available, a medicine was considered effective if results showed susceptibility, and was considered not effective if results showed resistance. Where DST results were missing, two situations existed. First, if the prevalence of resistance to that medicine was less than 10% in the same population (i.e. from the same country or study site if within one country, or overall at all sites if local data were not available), then the medicine was counted as effective. This situation applied to the following agents: cycloserine or terizidone, linezolid, clofazimine, bedaquiline, the carbapenems and delamanid. Second, if the prevalence of resistance to that medicine was more than or equal to 10% in the same population (from the same country or study site if within one country, or overall, at all sites if local data were not available), then imputed DST results were used to determine effectiveness if DST was missing. If the imputed DST result showed susceptibility, then the medicine was counted as effective; if the imputed DST result showed resistance, then the medicine was not counted as effective. This situation applied to the following agents: pyrazinamide, ethambutol, second-line injectable agents, fluoroquinolones, p-aminosalicylic acid, ethionamide and prothionamide. The following agents were not included when counting the number of medicines likely to be effective (regardless of any DST result that may have been available): isoniazid (including high-dose isoniazid), rifampicin, rifabutin, thioacetazone, amoxicillin–clavulanate and macrolide antibiotics.

Subsets of the main 2018 IPD meta-analysis with 13 104 patients overall from 53 studies in 40 countries were analysed for the risk of treatment failure and relapse versus success associated with different durations in these three recommendations on the duration of treatment (see **Web Annex 3** and **Web Annex 4** for the GRADE tables, and **Web Annex 6** for the analysis plan). Patients were followed up for relapse but numbers of patients reported with relapse were relatively small. The three IPD subsets for PICO questions 5, 6 and 7–2018 are discussed below.

PICO question 5–2018 (MDR/RR-TB, 2018) (different durations of the intensive phase)

The primary analysis used a subset of records from 3 750 patients from 42 observational studies; of these patients, 2 720 were treated with an individualized MDR-TB regimen and 1 030 were treated with standardized MDR-TB regimens. Of the 13 104 records in the main IPD, 9 354 records were excluded for the following reasons: lost to follow-up (*n*=2 261), died (*n*=2 043), did not receive an injectable (*n*=1 094), no information on duration of injectable (*n*=2 341), number of medicines likely to be effective less than five or less than four plus pyrazinamide (*n*=1 450) and duration of injectable longer than 20 months (*n*=165).

PICO question 6–2 018 (MDR/RR-TB, 2018) (on regimen duration)

The evidence to inform PICO question 6–2018 (MDR/RR-TB, 2018) was derived from a subset of 6 356 patients from 51 observational studies for the primary analysis. Of the 6 356 patients, 5 352 were treated with an individualized MDR-TB regimen and 1 004 were treated with a standardized MDR-TB regimen. Of the 13 104 records in the main IPD, 6 748 records were excluded for the following reasons: lost to follow-up (*n*=2 261), died (*n*=2 043), treatment duration not available (*n*=230), number of

effective drugs less than five or less than four plus pyrazinamide (*n*=2 072), treatment duration less than 6 months (*n*=52) and treatment duration more than or equal to 36 months (*n*=90).

PICO question 7–2018 (MDR/RR-TB, 2018) (on treatment duration after culture conversion)

The analysis to address PICO question 7–2018 (MDR/RR-TB, 2018) was derived from a subset of 4 175 patients from 39 observational studies. All but three of the 4 175 patients were on individualized regimens. The reasons for exclusion of 8 929 records from the main dataset were as follows: lost to follow-up (*n*=2 261), died (*n*=2 043), treatment duration not reported (*n*=230), culture information not reported (*n*=1 945), baseline culture negative (*n*=754), patient never culture converted (*n*=426), number of effective drugs less than five or less than four plus pyrazinamide (*n*=1 215), treatment duration less than 6 months (*n*=4), treatment duration more than or equal to 36 months (*n*=49) and culture converted post-treatment (*n*=2).

PICO question 1–2019 (MDR/RR-TB, 2019) (use of bedaquiline longer than 6 months)

To analyse treatment success, failure, relapse and death for the use of bedaquiline longer than 6 months, the data were derived from the endTB observational study, with the overall dataset comprising a total of 1 094 patients from 13 countries *(62)*.[28] The data analysed to answer this question were patients from the endTB observational study cohort who received bedaquiline for at least 6 months, had started bedaquiline within the first month of the treatment episode and did not receive delamanid concomitantly with bedaquiline during treatment; among patients with treatment success, data were from those who received at least 17.5 months of treatment overall. A total of 515 patients met these criteria. The intervention group comprised 242 patients who received bedaquiline for more than 203 days[29] overall, and they were compared to 273 patients who received bedaquiline for a total of 168–203 days. Additional data sources considered by the GDG 2019 included a cohort of 112 patients from Belarus treated with bedaquiline (of whom two had inadequate treatment information and were excluded), and a cohort of 123 patients from an MSF-managed clinic in Uzbekistan treated with bedaquiline (with one patient excluded due to inadequate treatment information). Of these 232 eligible patients, 65 received bedaquiline for more than 203 days and 72 received bedaquiline for 168–203 days. The primary analyses featured the endTB observational study data only.

PICO question 2–2019 (MDR/RR-TB, 2019) (use of bedaquiline and delamanid together)

To analyse treatment success, failure, relapse and death for the concurrent use of bedaquiline and delamanid, the data were derived from the same cohort of patients from the endTB observational study that informed PICO question 1–2019. However, in this dataset, only 92 patients received both medicines together for any period of time, and even fewer started bedaquiline and delamanid at the same time and within the first month of treatment (*n*=35). Another three patients were receiving concomitant bedaquiline and delamanid by the end of the first month of treatment, bringing the total number to 38. The remaining 57 patients started the two medicines more than 30 days apart and were therefore not included. Additional data sources comprised a cohort of 100 patients treated with bedaquiline in Mumbai, India (from an MSF-supported project), of whom 86 received some form of concomitant treatment with bedaquiline and delamanid during therapy; 62 of these 86 initiated the two medicines within 30 days of each other, and 46 of these 62 began both medicines during the first month of their treatment episode. The total intervention population therefore comprised 84 patients: 38 from the endTB observational study cohort and 46 from the Mumbai dataset. Because

[28] These countries are Armenia, Bangladesh, Belarus, the Democratic People's Republic of Korea, Ethiopia, Georgia, Indonesia, Kazakhstan, Kenya, Lesotho, Myanmar, Pakistan and Peru.

[29] 203 days was chosen as a cut-off as the intermodal trough of bedaquiline use for all patients in the endTB observational study was 203 days; the cut-off was not 6 months exactly, but 203 days.

the data available were limited, the sources of data for the comparator populations were derived from the endTB observational study, and the datasets from Belarus, Mumbai and Uzbekistan. There were inadequate numbers of patients available in the IPD for any meaningful analyses (*n*=4 patients who received bedaquiline and delamanid together). The primary comparison group included 401 patients (*n*=302 from the endTB observational study, *n*=82 from the Belarus dataset, *n*=17 from the Uzbekistan dataset and *n*=0 from the Mumbai dataset). These patients initiated bedaquiline within the first month of treatment and did not receive bedaquiline beyond 6 months duration. The secondary comparison group was derived from the endTB observational study and comprised 102 patients who received delamanid within the first month of treatment and who did not receive an extended duration of delamanid. No patients in the datasets from Belarus, Mumbai or Uzbekistan received delamanid for this duration. The median duration of concurrent use of bedaquiline and delamanid among the 84 patients in the intervention group was 18.5 months (IQR: 9 months, 21 months).

Additional data presented included safety data from the DELamanId Bedaquiline for ResistAnt TubErculosis (DELIBERATE) trial (AIDS Clinical Trials Group A5343). The DELIBERATE trial is a randomized, open-label, three-arm pharmacokinetic and safety trial conducted at study sites in Peru and South Africa. Eligible patients were aged 18 years and older, with pulmonary MDR-TB (or rifampicin monoresistance) receiving treatment for MDR-TB, but without clofazimine, and with moxifloxacin replaced by levofloxacin and a baseline QTcF of less than 450 ms. In addition to the MDR-TB treatment regimen with the conditions described above, the regimens used in the three study arms comprised the addition of bedaquiline 400 mg once daily for 2 weeks, then 200 mg thrice weekly for 22 weeks; the addition of delamanid 100 mg twice daily for 24 weeks; and the addition of both bedaquiline and delamanid. The primary objective of the trial was to compare the mean change from baseline in QTcF (averaged over weeks 8–24) when bedaquiline and delamanid were co-administered with the mean change observed when each drug was administered alone.

In addition to the data reviewed for PICO questions 1–2019 and 2–2019, the GDG 2019 was provided with and reviewed data from a study in South Africa on the use of bedaquiline during pregnancy. This observational cohort study included information from 108 pregnant women with RR-TB who were recruited from one MDR/RR-TB referral hospital in South Africa between January 2013 and December 2017. As part of their MDR/RR-TB regimen, 58 women received bedaquiline; they were compared with 50 women who had no bedaquiline in their regimen. The women in this study gave birth to 109 live infants, of whom 49 had bedaquiline exposure in utero and 60 had no bedaquiline exposure in utero. Clinical assessments were carried out at 2, 6 and 12 months after birth to document infant outcomes. The main objective of the study was to document treatment, pregnancy and infant outcomes among women treated for RR-TB with second-line TB drugs during pregnancy.

When reviewing evidence and formulating the recommendations, the GDG 2019 considered the need for the guidelines to also cater to key subgroups that were not well represented in the 2018 IPD meta-analysis – notably, children. Where data on children were unavailable, evidence from adults was extrapolated to children. The best available evidence was used to construct recommendations for a regimen that has high relapse-free cure rates, and that reduces the likelihood of death and the emergence of additional resistance while minimizing harms. The GDG 2019 was aware of the paediatric MDR-TB IPD meta-analysis on 975 clinically diagnosed or bacteriologically confirmed pulmonary or extrapulmonary TB cases that was used for the 2016 treatment recommendations *(56)*. Children with XDR-TB (pre-2021 definition) were excluded from that analysis (*n*=36) because their treatment regimens were not considered to be comparable with those of other MDR-TB patients, and their numbers were too low to be analysed independently. No RCTs were included (or known to exist) at the time this dataset was compiled, and the overall certainty in the estimates of effect based on this evidence was judged to be very low. However, in July 2019, preliminary data from the DELIBERATE trial were made available to the GDG 2019 to partly address PICO question 9; the overall certainty in the estimates of effect for this study was judged to be low.

PICO question 1–2021 (Childhood TB, 2021) (use of bedaquiline in MDR/RR-TB patients aged below 6 years)

To answer the PICO question on the use of bedaquiline in children aged below 6 years, data from two Phase 2 trials (TMC207-C211 and IMPAACT P1108) were reviewed by the GDG 2021. TMC207-C211 is a Phase 2, open-label, single-arm study to evaluate the pharmacokinetics, safety, tolerability and anti-mycobacterial activity of bedaquiline in combination with a background regimen of MDR-TB medications for the treatment of children and adolescents aged 0–17 years who have bacteriologically confirmed or clinically diagnosed pulmonary and selected forms of extrapulmonary MDR-TB.[30] IMPAACT P1108 is a Phase 1–2 dose finding modified age de-escalation study to evaluate the pharmacokinetics, safety and tolerability of bedaquiline in combination with optimized individualized MDR-TB regimens in children living with HIV and HIV-uninfected children with clinically diagnosed or confirmed pulmonary (intrathoracic) and selected forms of extrapulmonary MDR-TB.[31]

Data reviewed from TMC207-C211 corresponded to children aged 5–18 years and data from IMPAACT P1108 included children aged 0–6 years; therefore, the review of pharmacokinetics and safety data focused mainly on data from IMPAACT P1108. Although the sample size of the available interim data for review was small (n=12), the GDG 2021 concluded that in children aged 0–6 years, cardiac safety signals were not distinct from those reported in adults. Population pharmacokinetic models from both studies suggest that drug exposures observed in adults can be reached in most children receiving bedaquiline, although some dose modification may be necessary depending on the age and weight of the child.

In addition, data from a paediatric MDR/RR-TB IPD were analysed descriptively (24 231 records from all six WHO regions, the majority from India and South Africa). The search was conducted in April 2020. Just under 20 000 of these records were used for a matched analysis of treatment outcomes in children being treated for DR-TB. The analysis included 40 children aged below 6 years and 68 children aged 6–12 years who received bedaquiline. In the matched analysis, bedaquiline was significantly associated with shorter treatment duration and a lower aOR of injectable TB drug use. There was no statistically significant difference in successful treatment outcomes between children aged below 6 years receiving an all-oral bedaquiline-based regimen and those not receiving bedaquiline (89% vs 97%, P=0.9). Residual confounding (including confounding by indication) was thought to be likely.

A child-friendly formulation of bedaquiline (20 mg scored uncoated tablet) is being used in the Janssen C211 study to dose children aged below 5 years and will also soon be used in an updated protocol of the IMPAACT study P1108 (to date, this study has used the 100 mg formulation in all age groups). No head-to-head studies were conducted to examine the bioequivalence of the 20 mg and the 100 mg formulation of bedaquiline. Indirect bioequivalence testing showed that both tablets have the same bioavailability and can be used interchangeably at the same total dose. Findings from the bedaquiline crush study *(63)* also showed that the bioavailability of bedaquiline tablets suspended in water was the same as for tablets swallowed whole.

PICO question 2–2021 (Childhood TB, 2021) (use of delamanid in MDR/RR-TB patients aged below 3 years)

To answer the PICO question on the use of delamanid in children aged below 3 years, data were reviewed by the GDG 2021 from a Phase 1, open-label, age de-escalation trial designed to assess the pharmacokinetics, safety and tolerability of delamanid administered twice daily for 10 days in

[30] Pharmacokinetic study to evaluate anti-mycobacterial activity of TMC207 in combination with background regimen (BR) of multidrug resistant tuberculosis (MDR-TB) medications for treatment of children/adolescents pulmonary MDR-TB (https://clinicaltrials.gov/ct2/show/NCT02354014, accessed 21 January 2022).

[31] P1108. A Phase I/II, open-label, single arm study to evaluate the pharmacokinetics, safety and tolerability of bedaquiline (BDQ) in combination with optimized individualized multidrug-resistant tuberculosis (MDR-TB) therapy in HIV-infected and HIV-uninfected infants, children and adolescents with MDR-TB disease (https://www.impaactnetwork.org/studies/p1108, accessed 21 January 2022).

children with MDR/RR-TB on treatment with an optimized background regimen (protocol 242–12–232)[32] and from the corresponding open-label extension study (protocol 242–12–233).[33] Data from cohorts 1 (age 12–17 years), 2 (age 6–11 years), 3 (age 3–5 years) and 4 (age 0–2 years) for both protocols were reviewed. Exposures in the 0–2-year age group were lower than those of children aged 3 years and older, necessitating a modelling or simulation approach to dosing. No cardiac safety signals distinct from those reported in adults were observed in children aged 0–2 years. However, consideration of these findings should take into account that children had lower drug exposures than adults. Pharmacodynamic simulations suggested that clinically meaningful changes in QT (i.e. prolongation) would be unlikely in children aged below 3 years, even if higher doses were used to reach drug exposures comparable to those achieved in adults.

CNS effects (paraesthesia, tremors, anxiety, depression and insomnia) were included in the delamanid label for both adults and children as important potential safety concerns for the drug. In March 2021, the study sponsor released a statement of intent to modify the labelling to include hallucinations as an adverse reaction. This new safety signal has been more prevalent among children than adults, with 15 reports in 14 children aged 2–16 years in India, the Philippines, South Africa, Tajikistan and Ukraine. Children experiencing this safety signal included some with extensively resistant forms of TB (MDR/XDR-TB) treated with delamanid under programmatic conditions (12 reports) and children enrolled in a clinical trial studying delamanid for TB prevention (3 reports). Seven of the 15 reports were for children also receiving cycloserine (under programmatic conditions). The GDG noted the importance of side-effects involving the CNS in young children, considering their dynamic brain development.

In addition to data from the trials, data from a paediatric DR-TB IPD were analysed descriptively (24 231 records from all six WHO regions, the majority from India and South Africa). The search was conducted in April 2020. Just under 20 000 of these records were used for a matched analysis of treatment outcomes in children being treated for DR-TB. The paediatric DR-TB IPD included only seven children aged below 3 years treated with delamanid, 14 children aged 3–6 years and 69 children aged 6–12 years. All 21 children aged below 6 years were successfully treated. The number of children was insufficient for a matched analysis.

3.3 Remarks

The GDG 2018 assessed the individual contribution to patient outcomes of medicines used in longer MDR-TB regimens, using primarily the estimates of effect from the 2018 IPD meta-analysis and Trial 213 (delamanid) for PICO question 3–2018 (MDR/RR-TB, 2018) (see **Web Annex 3** for the respective GRADE summaries of evidence for each medicine, and **Web Annex 4** for the evidence-to-decision framework). Following a thorough assessment of the relative benefits and harms, recommendations were made for each medicine and they were classified into three groups (see **Table 3.1**, **Table 3.2** and **Table 3.3**).

- **Group A**: fluoroquinolones (levofloxacin and moxifloxacin), bedaquiline and linezolid were considered highly effective and strongly recommended for inclusion in all regimens unless contraindicated.
- **Group B**: clofazimine and cycloserine or terizidone were conditionally recommended as agents of second choice.
- **Group C**: included all other medicines that can be used when a regimen cannot be composed with Group A or Group B agents. The medicines in Group C are ranked by the relative balance of benefit to harm usually expected of each.

Other medicines that are not included in Groups A–C are as follows:

[32] Pharmacokinetic and safety trial to determine the appropriate dose for pediatric patients with multidrug resistant tuberculosis (https://clinicaltrials.gov/ct2/show/NCT01856634, accessed 21 January 2022).

[33] A 6-month safety, efficacy, and pharmacokinetic (PK) trial of delamanid in pediatric participants with multidrug resistant tuberculosis (MDR-TB) (https://clinicaltrials.gov/ct2/show/NCT01859923, accessed 21 January 2022).

- **Kanamycin and capreomycin** – these medicines were associated with poorer outcomes when used; therefore, they are no longer recommended for use in MDR-TB regimens.
- **Gatifloxacin and high-dose isoniazid, and thioacetazone** – gatifloxacin and high-dose isoniazid were used in only a few patients, and thioacetazone was not used at all. Currently, quality-assured preparations of gatifloxacin are not available, following its withdrawal from the market due to concerns about dysglycaemias. Thioacetazone is unlikely to have a role in contemporary longer regimens and is not currently available in a quality-assured formulation. High-dose isoniazid may have a role in patients with confirmed susceptibility to isoniazid (see **Section 3.4**).
- **Clavulanic acid** – this medicine should be included in MDR/RR-TB regimens only as a companion agent to the carbapenems (imipenem–cilastatin and meropenem). When used in this way, it should be given with every dose of carbapenem, and should not be counted as an additional effective TB agent.

No recommendation on perchlozone, interferon gamma or sutezolid was possible owing to the absence of final patient treatment outcome data from appropriate patient studies.

Regarding the use of bedaquiline in patients aged below 18 years, and considering that exposure–response (efficacy) profiles can be extrapolated from adults to children, the GDG concluded that the doses evaluated in children and adolescents in two trials (Phase 2 trial TMC207-C211 and Phase 1–2 IMPAACT P1108; see **Web Annex 5**) do not appear to result in exposures that would put patients aged 6–17 years at increased risk for treatment failure. The safety risk in children aged 6 years and older enrolled in the trials – all of whom were HIV-negative and had limited exposure to other QT interval-prolonging medications – did not appear to exceed that of adults. The variability present in the limited sample size precluded a comment on exposure–response (safety). The GDG 2018 also concluded that the risk–benefit considerations for the use of bedaquiline in patients aged 6–17 years are similar to those considered for adults; however, the GDG stressed the need for more data before considering upgrading this recommendation to "strong".

The GDG review in 2021 determined that the balance between desirable and undesirable effects probably favours the use of bedaquiline in children aged below 6 years. The GDG 2021 highlighted that the benefits may vary depending on specific contexts and population characteristics, such as by nutritional status. The GDG also noted that the potential higher cost of bedaquiline in an MDR/RR-TB treatment regimen should be considered in the context of the benefits of shorter injectable-free regimens (i.e. less travel, reduced time spent in clinics and fewer adverse events). In addition, they judged that equity might increase when bedaquiline becomes available to younger children, because its use would be acceptable to most stakeholders, and that one of the main feasibility aspects would be related to the need for safety monitoring (i.e. access to ECG monitoring, as well as staff capacity for monitoring). However, the panel judged that implementing the use of bedaquiline in young children was probably feasible.

With respect to the use of delamanid in children aged below 6 years, the GDG review in 2018 decided that – based on findings in adults, and on the pharmacological and safety data reviewed – extrapolations on efficacy and safety should be restricted to children aged 3–5 years, but not to children aged below 3 years (see **Web Annex 5**). Exposure profiles in children aged 3–5 years were comparable to adults, and were no higher than in children aged 6 years and older, for whom past GDGs convened by WHO had already recommended the use of delamanid *(10, 64)*. Based on the laboratory and cardiac data provided, no safety signals distinct from those reported in adults were observed in children aged 3–5 years. The GDG nonetheless had concerns about the feasibility of administering the correct dose to children aged 3–5 years, given that the special formulation used in the trial (25 mg) would not be available in the foreseeable future, and that only the adult tablet (50 mg) is available, which is not bioequivalent and presents challenges to manipulating its contents without compromising its effectiveness.

The GDG review in 2021 concluded that the balance between desirable and undesirable effects probably favours the use of delamanid in children aged below 3 years. The GDG 2021 further stated

that when the 25 mg dispersible tablet became available in the future, the resource implications could vary. It was thought that delamanid containing longer treatment regimens could potentially increase equity and be acceptable to stakeholders. In addition, the GDG 2021 judged that it would probably be feasible to use delamanid in children of all ages, especially as the child-friendly formulation of delamanid was expected to become available later in 2021 (this formulation is now available). This judgement also considered that adult tablets cannot be split, crushed or dissolved to ease administration in children without potentially altering bioavailability.

As a result of these multiple reviews as new data have gradually become available, the use of bedaquiline and delamanid are no longer restricted by the age of the patient.

Table 3.1. Grouping of medicines recommended for use in longer MDR-TB regimens[a]

Groups and steps	Medicine	Abbreviation
Group A: Include all three medicines	Levofloxacin *or* moxifloxacin	Lfx Mfx
	Bedaquiline[b,c]	Bdq
	Linezolid[d]	Lzd
Group B: Add one or both medicines	Clofazimine	Cfz
	Cycloserine *or* terizidone	Cs Trd
Group C: Add to complete the regimen and when medicines from Groups A and B cannot be used	Ethambutol	E
	Delamanid[e]	Dlm
	Pyrazinamide[f]	Z
	Imipenem–cilastatin *or* meropenem[g]	Ipm–Cln Mpm
	Amikacin (*or* streptomycin)[h]	Am (S)
	Ethionamide *or* prothionamide[i]	Eto Pto
	P-aminosalicylic acid[i]	PAS

DST: drug susceptibility testing; ECG: electrocardiogram; GDG: Guideline Development Group; IPD: individual patient data; LPA: line probe assay; MDR-TB: multidrug-resistant TB; TB: tuberculosis.

[a] This table is intended to guide the design of individualized, longer MDR-TB regimens (the composition of the recommended shorter MDR-TB regimen is largely standardized; see **Section 2**). Medicines in Group C are ranked by decreasing order of usual preference for use, subject to other considerations. The 2018 IPD meta-analysis for longer regimens included no patients on thioacetazone and too few patients on gatifloxacin and high-dose isoniazid for a meaningful analysis. No recommendation on perchlozone, interferon gamma or sutezolid was possible owing to the absence of final patient treatment outcome data from appropriate studies (see **Web Annex 5**).

[b] Bedaquiline is usually administered at 400 mg orally once daily for the first 2 weeks, followed by 200 mg orally three times per week for 22 weeks (total duration of 24 weeks). As a result of multiple reviews as new data have gradually become available, the use of bedaquiline is no longer restricted by the age of the patient. Evidence on the safety and effectiveness of bedaquiline use beyond 6 months was insufficient for review in 2018. Therefore, the use of bedaquiline beyond 6 months was implemented following best practices in "off-label" use *(65)*. New evidence on the safety profile of bedaquiline use beyond 6 months was available to the GDG 2019, but the GDG was not able to assess the impact of prolonged bedaquiline use on efficacy, owing to the limited evidence and potential residual confounding in the data. However, the evidence supports the safe use of bedaquiline beyond 6 months in patients who receive appropriate schedules of baseline and follow-up monitoring. The use of bedaquiline beyond 6 months remains as off-label use and, in this regard, best practices in off-label use still apply.

[c] Evidence on the concurrent use of bedaquiline and delamanid was insufficient for review in 2018. In 2019, new evidence on the concurrent use of bedaquiline and delamanid was made available to the GDG. Regarding safety, the GDG concluded that the data suggest no additional safety concerns regarding concurrent use of bedaquiline and delamanid. Both medicines may be used concurrently in patients who have limited other treatment options available to them, provided that sufficient monitoring (including baseline and follow-up ECG and electrolyte monitoring) is in place. The data on the effectiveness of concurrent use of bedaquiline and delamanid were reviewed by the GDG; however, owing to the limited evidence and potential residual confounding in the data, the GDG was unable to proceed with a recommendation on effectiveness.

[d] Use of linezolid for at least 6 months was shown to increase effectiveness, although toxicity may limit use. The analysis suggested that using linezolid for the entire duration of treatment would optimize its effect (about 70% of patients on linezolid with data received it for >6 months and 30% for 18 months or the entire duration). No patient predictors for early cessation of linezolid could be inferred from the IPD subanalysis.

[e] Evidence on the safety and effectiveness of delamanid beyond 6 months was insufficient for review. The use of delamanid beyond these limits should follow best practices in "off-label" use *(65)*. As a result of multiple reviews as new data have gradually become available, the use of delamanid is no longer restricted by the age of the patient.

[f] Pyrazinamide is counted as an effective agent only when DST results confirm susceptibility.

[g] Every dose of imipenem–cilastatin and meropenem is administered with clavulanic acid, which is available only in formulations combined with amoxicillin. Amoxicillin–clavulanic acid is not counted as an additional effective TB agent and should not be used without imipenem–cilastatin or meropenem.

[h] Amikacin and streptomycin are to be considered only if DST results confirm susceptibility, and if high-quality audiometry monitoring for hearing loss can be ensured. Streptomycin is to be considered only if amikacin cannot be used (i.e. if it is unavailable or there is documented resistance) and if DST results confirm susceptibility (i.e. resistance to streptomycin is not detectable with second-line molecular LPAs and phenotypic DST is required). Kanamycin and capreomycin are no longer recommended for use in MDR-TB regimens.

[i] These agents showed effectiveness only in regimens without bedaquiline, linezolid, clofazimine or delamanid, and are thus proposed only when other options to compose a regimen are not possible.

Table 3.2. Relative risk for treatment failure or relapse, and death (versus treatment success), 2018 IPD meta-analysis for longer MDR-TB regimens and delamanid Trial 213 (intent-to-treat population)[a]

Medicine		Treatment failure or relapse versus treatment success		Death versus treatment success	
		Number treated	Adjusted odds ratio (95% CL)	Number treated	Adjusted odds ratio (95% CL)
A	Levofloxacin *or* moxifloxacin	3 143	0.3 (0.1–0.5)	3 551	0.2 (0.1–0.3)
	Bedaquiline	1 391	0.3 (0.2–0.4)	1 480	0.2 (0.2–0.3)
	Linezolid	1 216	0.3 (0.2–0.5)	1 286	0.3 (0.2–0.3)
B	Clofazimine	991	0.3 (0.2–0.5)	1 096	0.4 (0.3–0.6)
	Cycloserine *or* terizidone	5 483	0.6 (0.4–0.9)	6 160	0.6 (0.5–0.8)

Medicine		Treatment failure or relapse versus treatment success		Death versus treatment success	
		Number treated	Adjusted odds ratio (95% CL)	Number treated	Adjusted odds ratio (95% CL)
C	Ethambutol	1 163	0.4 (0.1–1.0)	1 245	0.5 (0.1–1.7)
	Delamanid	289	1.1 (0.4–2.8)[b]	290	1.2 (0.5–3.0)[b]
	Pyrazinamide	1 248	2.7 (0.7–10.9)	1 272	1.2 (0.1–15.7)
	Imipenem–cilastatin *or* meropenem	206	0.4 (0.2–0.7)	204	0.2 (0.1–0.5)
	Amikacin	635	0.3 (0.1–0.8)	727	0.7 (0.4–1.2)
	Streptomycin	226	0.5 (0.1–2.1)	238	0.1 (0.0–0.4)
	Ethionamide *or* prothionamide	2 582	1.6 (0.5–5.5)	2 750	2.0 (0.8–5.3)
	P-aminosalicylic acid	1 564	3.1 (1.1–8.9)	1 609	1.0 (0.6–1.6)
Other medicines	Kanamycin	2 946	1.9 (1.0–3.4)	3 269	1.1 (0.5–2.1)
	Capreomycin	777	2.0 (1.1–3.5)	826	1.4 (0.7–2.8)
	Amoxicillin–clavulanic acid	492	1.7 (1.0–3.0)	534	2.2 (1.3–3.6)

CL: confidence limits; GDG: Guideline Development Group; IPD: individual patient data; MDR-TB: multidrug-resistant tuberculosis.

[a] See also text, **Table 3.3** and **Web Annex 3**, **Web Annex 4** and **Web Annex 5** for more detail on how the estimates were derived and the additional factors considered by the GDG when reclassifying medicines for use in longer MDR-TB regimens, as shown in **Table 3.1**.

[b] The values are the unadjusted risk ratios, as defined by the study investigators of Trial 213 by month 24.

PICO question 4–2018 (MDR/RR-TB, 2018) (number of agents likely to be effective)

Regarding PICO question 4–2018 (MDR/RR-TB, 2018), the analysis showed that in longer MDR-TB treatment regimens, the risk of treatment failure, relapse and death was comparable when the treatment started with four, five or six medicines that were likely to be effective. It also showed that patients who took three agents in the continuation phase – the situation expected when starting with four agents and stopping the injectable agent at the end of the intensive phase – fared no worse than those who took four agents in the continuation phase.

Given that drug–drug interactions, pill burden and likelihood of adverse events all increase with the number of agents in a regimen, it would be desirable to give patients the minimum number of medicines necessary to obtain comparable levels of relapse-free cure. When deciding on the minimum number of agents to recommend, the GDG 2018 considered analyses that included injectable agents in the regimens, while fully cognizant that future longer regimens are expected to be increasingly injectable free. Moreover, it was important to provide for situations in which more than one medicine is stopped at some point during treatment, either because of its indication for use – bedaquiline and delamanid on-label use is 6 months – or because of tolerability (particularly linezolid; **Table 3.3**) *(66)*;

hence, for most of its duration, the regimen would contain two key agents fewer than at the start. Although bedaquiline use beyond 6 months is referred to as off-label use, new evidence on the safety profile of bedaquiline use beyond 6 months was available to the GDG 2019. This evidence supports the safe use of bedaquiline beyond 6 months in patients who receive appropriate schedules of baseline and follow-up monitoring. The use of bedaquiline beyond 6 months continues to be off-label use; thus, best practices in off-label use still apply.

The 2018 IPD included experience from more than 300 patients who were treated with linezolid for at least 1 month, mostly at a dose of 600 mg/day, with information on duration of use. About 30% only received linezolid for 1–6 months, but more than 30% received it for more than 18 months, and these patients had the lowest frequency of treatment failure, loss to follow-up and death. A plot of linezolid duration and treatment failure suggests that the optimal duration of use would be about 20 months, corresponding to the usual total duration of a longer MDR-TB regimen. However, such an analysis does not account for survivorship bias, meaning that those who complete the full length of treatment are more likely to have a successful outcome, given that deaths and losses to follow-up occur earlier. No clear pattern could be discerned for type of adverse event and duration of use, although a few cases were reported with optic neuropathy, known to be associated with long-term use of linezolid *(67)*, whereas haematological toxicity was reported regardless of duration of use.

Table 3.3. Serious adverse events in patients on longer MDR-TB regimens[a]

Medicine	Absolute risk of serious adverse event	
	Median (%)	95% credible interval
Bedaquiline	2.4	[0.7, 7.6]
Moxifloxacin	2.9	[1.4, 5.6]
Amoxicillin–clavulanic acid	3.0	[1.5, 5.8]
Clofazimine	3.6	[1.3, 8.6]
Ethambutol	4.0	[2.4, 6.8]
Levofloxacin	4.1	[1.9, 8.8]
Streptomycin	4.5	[2.3, 8.8]
Cycloserine or terizidone	7.8	[5.8, 10.9]
Capreomycin	8.4	[5.7, 12.2]
Pyrazinamide	8.8	[5.6, 13.2]
Ethionamide or prothionamide	9.5	[6.5, 14.5]
Amikacin	10.3	[6.6, 17.0]
Kanamycin	10.8	[7.2, 16.1]
P-aminosalicylic acid	14.3	[10.1, 20.7]
Thioacetazone	14.6	[4.9, 37.6]
Linezolid	17.2	[10.1, 27.0]

GDG: Guideline Development Group; IPD: individual patient data; MDR-TB: multidrug-resistant TB; TB: tuberculosis.

[a] From an "arm-based network" meta-analysis of a patient subset from the 2016 IPD for which adverse events resulting in permanent discontinuation of a TB medicine (27 studies) or classified as Grade 3–5 (three studies) were reported. There are slight differences between the final estimates cited in the resultant publication *(66)* and the values derived at the time of the GDG and shown in this table, because an expanded dataset was used in the publication; however, the slight differences have no impact on the conclusions drawn on the use of these medicines. There were insufficient records on delamanid, imipenem–cilastatin and meropenem to estimate risks. Agents that are not in Groups A, B or C are italicized.

In 2018, the GDG recommended that, where possible, regimens be composed of all three Group A agents and at least one Group B agent, so that treatment starts with at least four medicines likely to be effective, and that at least three agents are continued for the remaining duration of treatment if bedaquiline is stopped after 6 months. New evidence on the safety profile of bedaquiline use beyond 6 months was available to the GDG 2019. This evidence supports the safety of using bedaquiline beyond 6 months in patients who receive appropriate schedules of baseline and follow-up monitoring. If only one or two Group A agents can be used, both Group B agents are included. If the regimen cannot be composed with agents from Groups A and B alone, Group C agents are added to complete it. **For patients in whom two agents from Group A are more likely to be stopped before the end of treatment (e.g. pre-existing comorbidities require that both bedaquiline and linezolid be stopped early because of health risks), then starting with five effective agents rather than four may be advisable.** These provisions are expected to apply to most MDR/RR-TB patients, including those with additional resistance to fluoroquinolones or other medicines.

PICO question 8–2019 (MDR/RR-TB, 2019) (use of bedaquiline longer than 6 months)

Regarding PICO question 8–2019 (MDR/RR-TB, 2019), the analysis yielded aORs of 1.5 (95% CI: 0.7–2.7) for treatment success versus failure, 0.8 (95% CI: 0.2–0.4) for treatment success versus death, 1.0 (95% CI: 0.5–1.7) for treatment success versus failure or death, and 0.8 (95% CI: 0.5–1.2) for treatment success versus all unfavourable outcomes. The evidence reviewers had planned to use two analytical approaches designed to minimize bias; that is, marginal structural models to account for time-varying confounders, and for exact and propensity score matching of patient characteristics. However, sample size meant that there were limitations in how the first approach could be applied; also, owing to limitations with the dataset, biostatisticians advised that it was not possible to adjust for confounders according to the original data analysis plan. The GDG 2019 noted that the population included in the studies that were assessed was highly selected, with the potential for confounding by indication (i.e. the people who received bedaquiline for >6 months were likely to have done so because of clinical factors that indicated prolonged treatment with bedaquiline). The GDG concluded that there was a high likelihood of residual confounding in the data, and that the patient population addressed in the study did not permit extrapolation to routine use in all MDR/RR-TB patients. This precluded a formal recommendation on the efficacy or effectiveness of bedaquiline use beyond 6 months duration; however, the GDG 2019 concluded that a statement on safety could be made. This information is included in **Section 3.5** and in a table note for **Table 3.1**.

Regarding **adverse events**, among the 750 patients receiving bedaquiline without concomitant delamanid in the endTB observational study (total exposure of 6 316 person-months), 26 patients experienced a drug-related adverse event (rate: 0.44 per 100 person-months of exposure), with 16 patients having this event classified as a serious adverse event (rate: 0.25 per 100 person-months of exposure). In the first 203 days of exposure to bedaquiline (total exposure of 4 304 person-months), 20 of the 26 drug-related adverse events and 15 of the 16 serious adverse events occurred; the remaining six of the 26 drug-related adverse events and one of the 16 serious adverse events occurred subsequently. All patients who received bedaquiline for more than 203 days did not experience a drug-related adverse event (of any grade) in the first 203 days of treatment. Also, rates of treatment drug-related adverse events appeared to be lower after the first 203 days – at 0.51 in the first 203 days versus 0.30 in the subsequent days per 100 person-months. Similarly, rates of drug-related serious adverse events appeared to be lower after the first 203 days – at 0.35 in the first 203 days versus 0.05 in the subsequent days per 100 person-months.

QTcF values among people receiving bedaquiline increased by an average of 22 ms (from 397 ms to 419 ms) from those taken before or at the time of first receipt of bedaquiline to the end of the first month. In subsequent months of exposure, the mean QTcF values were all lower than at the end of the first month (range: 404–419 ms). Increases in QTcF of more than 60 ms from baseline occurred in about 12% of patients. QTcF prolongation of more than 500 ms was rare, occurring in 0.4–1.5% of

patients during each of the first 9 months, but not thereafter. The greatest number of occurrences of QTcF of more than 500 ms happened among people receiving bedaquiline and clofazimine; however, this was also the most common combination of medicines received.

Drug-related cardiac adverse events occurred in 22 people; of these, 15 were among people receiving bedaquiline with clofazimine, but no moxifloxacin or delamanid (rate: 0.3 per 100 person-months), five were among people receiving bedaquiline with clofazimine and moxifloxacin, but no delamanid (rate: 0.3 per 100 person-months), and two were among people receiving bedaquiline and delamanid, regardless of clofazimine and moxifloxacin use (rate: 0.2 per 100 person-months). No events occurred among people receiving bedaquiline without clofazimine, moxifloxacin and delamanid.

Regarding **bedaquiline exposure during pregnancy**, the findings of the cohort study demonstrated no statistically significant differences in birth or pregnancy outcomes when comparing infants who had intrauterine bedaquiline exposure with those who did not have this exposure (*P*=0.741 for birth outcomes and *P*=0.312 for pregnancy outcomes) *(51)*. There were 45 live births (92% of total) in the bedaquiline exposed group compared with 54 live births (90% of total) in the unexposed group. In addition, there were four fetal and neonatal deaths in the infants exposed to bedaquiline (8% of the total bedaquiline exposed group, with three stillbirths and one termination of pregnancy) and six fetal and neonatal deaths in the bedaquiline unexposed group (10% of the total unexposed group, comprising three stillbirths and three miscarriages) *(51)*. The results of the study also demonstrated that treatment outcomes were favourable for pregnant women exposed to bedaquiline compared with those not exposed (71% vs 62%, respectively, *P*=0.349) *(51)*. Pregnancy outcomes included live births and unfavourable pregnancy outcomes (fetal and neonatal deaths, preterm births <37 weeks and low birth weight <2 500 g); infant outcomes included weight gain and developmental milestones and the diagnosis of TB *(51)*. Of all pregnancy and infant outcomes assessed, only low birth weight was associated with bedaquiline exposure in utero (45% vs 26%, *P*=0.034). The average weight in bedaquiline exposed infants was 2 690 g versus 2 900 g in infants not exposed to bedaquiline. However, it was not possible to conclusively ascribe this effect to bedaquiline, and more investigation is needed to explore this relationship *(51)*. There were no significant differences in infant growth after birth: in a subanalysis of 86 babies followed up prospectively – 41 exposed to bedaquiline in utero and 45 not exposed – 88% of babies exposed to bedaquiline in utero had normal weight gain at 1 year of age versus 82% of babies not exposed (*P*=0.914) *(51)*.

PICO question 9–2019 (MDR/RR-TB, 2019) (use of bedaquiline and delamanid together)

Regarding PICO question 9 (MDR/RR-TB, 2019), the analyses yielded aORs of 1.6 (95% CI: 0.5–5.4) for treatment success versus treatment failure, 0.8 (95% CI: 0.3–2.1) for treatment success versus death, 1.2 (95% CI: 0.6–2.5) for treatment success versus failure or death, and 0.6 (95% CI: 0.3–1.1) for treatment success versus all unfavourable outcomes. Regarding adverse events, among the 92 patients receiving bedaquiline with concomitant delamanid during treatment in the endTB observational study (total exposure of 1 095 person-months), two bedaquiline-related adverse events and delamanid-related adverse events occurred (combined rate: 0.46 per 100 person-months of exposure). This rate was comparable to the rates among people receiving bedaquiline alone (0.41 per 100 person-months of exposure) and delamanid alone (0.68 per 100 person-months of exposure). Two drug-related serious adverse events occurred among the 92 patients receiving concomitant bedaquiline and delamanid, one attributed to each drug (combined rate: 0.09 per 100 person-months of exposure). The rate of these events was lower than the rates of drug-related serious adverse events among patients receiving either of these drugs alone (bedaquiline, 0.28; delamanid, 0.39). No fatal drug-related events occurred among patients receiving bedaquiline and delamanid concurrently.

QTcF values among people receiving bedaquiline and delamanid increased by an average of 15 ms (from 398 ms to 413 ms) from those taken before or at the time of first receipt of concurrent bedaquiline and delamanid use, to the end of the first month. In subsequent months of exposure, the mean QTcF values were similar to those at the end of the first month (range: 404–420 ms). QTcF

prolongation of more than 500 ms was rare, occurring in only one patient in month 7 of concomitant exposure. Drug-related cardiac adverse events were infrequent, occurring in only two of 92 people exposed to concomitant bedaquiline and delamanid (rate: 0.2 per 100 person-months). Only one drug-related cardiac serious adverse event occurred (rate: 0.1 per 100 person-months). No fatal drug-related cardiac events occurred among the 92 people exposed to bedaquiline and delamanid concurrently.

In the endTB observational study overall (*n*=1 094), there were two fatal drug-related cardiac events (sudden deaths attributable to QT prolongation), and one other patient experienced a cardiac arrhythmia. The two deaths occurred among patients receiving bedaquiline, clofazimine, capreomycin and *p*-aminosalicylic acid (but not moxifloxacin or delamanid); in both patients, hypokalaemia was present. These patients were not included in the analysis related to this PICO question because they did not meet the criteria for inclusion according to the predefined statistical analysis plan. However, recognizing that these estimates of serious adverse events were absolute and not relative, the panel felt that this additional evidence was important for close monitoring when the final data of the endTB observational study become available.

The GDG agreed that there was insufficient evidence to assess the efficacy or effectiveness of the concomitant use of bedaquiline and delamanid, given that there were only 84 patients in the intervention group and the data did not lend themselves to a meaningful analysis for the secondary comparator (extended use of delamanid alone) because the populations were too different to allow for the matching that is usually carried out. This precluded a formal recommendation on the efficacy or effectiveness of the concomitant use of bedaquiline and delamanid; however, the GDG concluded that a statement on safety could be made. This information is included in **Section 3.5** and in a table note for **Table 3.1**.

Additional data presented from the DELIBERATE trial highlighted that – among the patients randomized to bedaquiline (*n*=28), delamanid (*n*=27) or both medicines (*n*=27) – the on-treatment change in QTcF from baseline was 11.9 ms, 8.6 ms and 20.7 ms, respectively.[34] Of the 27 patients who received both medicines, 10 (37.0%) experienced a Grade 1[35] QT prolongation adverse event, and two (7.4%) experienced a Grade 2 QT adverse event. In the bedaquiline arm, 32.0% and 3.6% of patients experienced Grade 1 and 2 QT adverse events; in the delamanid arm, these figures were 41.0% for a Grade 1 QT adverse event and 7.4% for a Grade 2 QT adverse event. No patients experienced Grade 3 or 4 QT adverse events. The study investigators concluded that the QTcF prolongation effects of concurrent delamanid and bedaquiline use were not greater than their additive effects. The GDG noted that the QT adverse events in the DELIBERATE trial were surrogate markers of sudden cardiac death. They also noted that levofloxacin was the fluoroquinolone of choice in regimens given to patients in the DELIBERATE trial and that serum potassium was closely monitored.

PICO question 1–2021 (Childhood TB 2021) (use of bedaquiline in MDR/RR-TB patients aged below 6 years) and PICO question 2–2021 (Childhood TB 2021) (use of delamanid in MDR/RR-TB patients aged below 3 years)

Regarding PICO question 1–2021 (Childhood TB 2021) and PICO question 2–2021 (Childhood TB 2021), the details of the evidence review and GDG deliberations can be found in Module 5. Management of tuberculosis in children and adolescents.

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[34] Personal communication, K Dooley, Johns Hopkins Medicine, November 2019 – for this statement and the rest of this paragraph.

[35] In the DELIBERATE trial, a Grade 1 QT adverse event was classified as an absolute QTcF in the following situations: >480 ms and ≤500 ms and QTcF change from baseline from >0 ms to ≤30 ms *OR* an absolute QTcF ≤480 ms and QTcF change from baseline from >30 ms to ≤60 ms. A Grade 2 QT adverse event was classified as an absolute QTcF in the following situations: >480 ms and ≤500 ms and QTcF change from baseline from >30 ms to ≤60 ms *OR* an absolute QTcF ≤480 ms and QTcF change from baseline >60 ms. A Grade 3 QT adverse event was classified as an absolute QTcF in the following situation: >500 ms *OR* an absolute QTcF >480 ms and QTcF change from baseline >60 ms. A Grade 4 QT adverse event was a life-threatening consequence; for example, torsade des pointes or other associated serious ventricular dysrhythmia (personal communication, K Dooley, Johns Hopkins Medicine, November 2019).

3.4 Subgroup considerations

MDR/RR-TB alone or with additional resistance

A longer regimen is used where a shorter regimen cannot be used; it is more likely to be effective if its composition is guided by reliable information on drug susceptibility. The design of longer regimens for MDR/RR-TB patients with additional resistance follows a similar logic to that used for other MDR/RR-TB patients. All MDR/RR-TB patients should be tested for resistance to fluoroquinolones as a minimum before starting MDR-TB treatment. If the use of amikacin is being considered in the regimen, then rapid testing for second-line injectable agents should be performed. Other tests that may help to inform regimen choice and composition are those for resistance to agents such as bedaquiline, delamanid, linezolid and pyrazinamide, and for mutation patterns commonly associated with resistance to isoniazid and ethionamide or prothionamide. In many settings, DST for other medicines commonly used for MDR-TB treatment is not usually reliable enough to guide regimen composition. Because of this, other elements may be necessary to determine the likelihood of effectiveness (see **Section 3.5**). NTPs should possess or rapidly build the capacity to undertake DST, and all efforts should be made to ensure access to approved rapid molecular tests. Until the capacity for second-line DST – including for bedaquiline, linezolid and clofazimine – becomes available, treatment decisions may need to rely on the likelihood of resistance to medicines, based on an individual patient's clinical history and surveillance data from the country or region.

The analysis for the three PICO questions on the duration of treatment did not show any differences overall in treatment failure or relapse when comparing patients with MDR-TB with or without additional second-line drug resistance, including those with additional resistance to fluoroquinolones and injectable agents. In patients with resistance to amikacin and streptomycin, Recommendation 3.17 does not apply. The duration of treatment may need to be longer than 20 months overall in MDR/RR-TB cases with extended resistance patterns, subject to the clinical response to treatment.

Rifampicin-resistant TB

A patient (child or adult) in whom isoniazid resistance is absent needs to be treated with a recommended MDR-TB regimen – either a longer MDR-TB regimen to which isoniazid is added, or a shorter MDR-TB regimen in eligible patients (see also **Sections 1** and **2**). Although high-dose isoniazid is not included in Groups A–C, given the rarity of its use in contemporary longer regimens for adults with MDR/RR-TB, it may still be used in patients with confirmed susceptibility or in the presence of mutations that do not usually confer complete resistance to isoniazid *(68)*. High-dose isoniazid was shown to be an important component in paediatric regimens in a 2016 evidence review of the WHO guidelines; based on this finding its use in adults was extrapolated *(56)*. In this analysis, high-dose isoniazid was associated with treatment success among children with confirmed MDR-TB (aOR: 5.9, 95% confidence limits [CL]: 1.7–20.5, P=0.007).

Children

The 2018 IPD of longer regimens comprised mainly data from adult patients, with only 181 of the 13 104 (1.4%) cases being in children and adolescents aged below 15 years. Nonetheless, WHO recommendations on longer MDR-TB regimens apply to children as well as adults. Most medicines that are used in longer regimens have been part of MDR-TB regimens for many years, in similar combinations, for both adults and children. The GDG 2021 recommended the use of bedaquiline and delamanid in children of all ages *(31)*. Reproducing the delamanid exposure achieved with the special 25 mg tablet tested in the trial in children aged 3–5 years is expected to be challenging, given that this formulation is not bioequivalent with the 50 mg delamanid adult tablet – the only preparation available at that time *(12)*. There are also concerns that the adult tablet may shatter if attempts are made to split it, and that its contents are exceedingly bitter and unpalatable. Further,

bioavailability may be altered when the 50 mg tablet is split, crushed or dissolved. Delamanid is susceptible to oxidation and heat; therefore, retaining pill fragments for use at a time other than the time of initial administration is likely to result in the delivery of lower-than-expected active compound and unspecified oxidation by-products.

The avoidance of an injectable-containing regimen is particularly desirable in children, especially those who are very young and those with mild disease (as determined by the absence of malnutrition), serious forms of extrapulmonary disease, cavitation on chest radiography or HIV infection. Hearing loss can have a permanent effect on the acquisition of language and the ability to learn at school; therefore, if amikacin or streptomycin use is resorted to in children, regular audiometry is required.

The recommendations on treatment duration apply also to children. Given that many patients in the paediatric age group may only be clinically diagnosed or have extrapulmonary disease, it is expected that treatment duration will largely be guided by Recommendation 3.15, subject to response to treatment. Shortening the total treatment duration to less than 18 months may be considered in the case of children without extensive disease (see **Definitions**).

Extrapulmonary TB and TB meningitis

The WHO recommendations on longer MDR-TB regimens apply also to patients with extrapulmonary disease. Adjustments may be required, depending on the specific location of the disease. Treatment of MDR/RR-TB meningitis is best guided by DST of the infecting strain and by knowledge of the properties of TB medicines that cross the blood–brain barrier. Levofloxacin and moxifloxacin penetrate the CNS well *(69)*, as do ethionamide or prothionamide, cycloserine or terizidone, linezolid and imipenem–cilastatin *(70, 71)*. Seizures may be more common in children with meningitis treated with imipenem–cilastatin; thus, meropenem is preferred for meningitis cases and in children. High-dose isoniazid and pyrazinamide can also reach therapeutic levels in the cerebrospinal fluid, and they may be useful if the strains are susceptible. *P*-aminosalicylic acid and ethambutol do not penetrate the CNS well, and they should not be counted on as effective agents for MDR/RR-TB meningitis. Amikacin and streptomycin penetrate the CNS only in the presence of meningeal inflammation. There are few data on the CNS penetration of clofazimine, bedaquiline or delamanid *(72–74)*. In addition, cerebrospinal fluid concentrations may not mirror concentrations in the meninges or brain.

Pregnancy

Amikacin, streptomycin, prothionamide and ethionamide are usually contraindicated during pregnancy. Because of the potential for teratogenic effects from these medications, including the injectable agents, Recommendation 3.17 is of limited relevance in this subgroup. Following the changes made in the 2018 guidelines update, these agents are expected to be used less frequently in longer regimens. Knowledge about the safety of bedaquiline and delamanid in pregnancy and breastfeeding is sparse. However, new evidence from an observational study in South Africa was presented to the GDG 2019; it included information on 58 mothers who received bedaquiline during pregnancy *(51)*. The results of this study indicated that fetal exposure to bedaquiline in utero was associated with low birth weight[36] (45% of babies exposed to bedaquiline had a low birth weight compared with 26% of babies not exposed, *P*=0.034) *(51)*. However, there were no other significant differences in infant outcomes, pregnancy outcomes or maternal treatment outcomes, including weight gain in the infants until 1 year of age *(51)*. In such cases, it is recommended that a longer regimen be individualized to include components with a better established safety profile. The outcomes of treatment and pregnancy, including data from postpartum surveillance for congenital anomalies, should be documented to help inform future recommendations for MDR-TB treatment during pregnancy.

[36] Low birth weight was defined as less than 2 500 g.

HIV infection

The composition of the treatment regimen for MDR-TB does not usually differ substantially for PLHIV. With careful attention, it is possible to avoid certain drug–drug interactions (e.g. bedaquiline and efavirenz; see also the HIV drug interactions website of the University of Liverpool *(36)*).

Patients with extensive pulmonary TB disease

The duration of treatment post culture conversion may be modified according to the patient's response to therapy[37] (e.g. culture conversion before 2 months of treatment) and other risk factors for treatment failure or relapse. This should be considered in patients with extensive TB disease.

Patients on regimens without amikacin or streptomycin

In patients on regimens that do not contain injectable agents in the intensive phase, Recommendation 3.17 does not apply, and the length of treatment is determined by recommendations on total duration and on time after culture conversion (i.e. Recommendations 3.15 and 3.16). In the future, this situation is expected to apply to an increasing proportion of patients who are treated with oral-only regimens. If bedaquiline or other agents (e.g. linezolid or delamanid) are given only for the initial part of a regimen, this period does not equate to an "intensive phase" unless an injectable agent is used concurrently, as premised by the meta-analysis that informed Recommendation 3.17.

3.5 Implementation considerations

The new recommendations signal an important departure from previous approaches to treating MDR/RR-TB. The implementation of MDR/RR-TB treatment on a large scale is feasible under programmatic conditions, as has been shown by the global expansion in the use of standardized and individualized MDR-TB regimens in low-, middle- and high-income countries worldwide, particularly in the past decade *(1)*. The 2018 revision of the guidelines brought important changes to the grouping of medicines, the composition of longer MDR-TB regimens and the duration of medicine use, but it is expected that implementation of these changes will be feasible. The rapidity with which the new recommendations are applied in (or to) programmes may be influenced by a range of factors, but these should not stand in the way of increased access to life-saving treatment for patients who need it.

All of the agents recommended for use are available via the GDF, and most are also available in quality-assured, affordable generic formulations from other sources. Bedaquiline was available via a donation programme until March 2019; it is now available via the GDF, and a decrease in price has been negotiated with the manufacturer for low-resource settings. The evidence assessed during the GDG meeting in November 2019 did not allow the group to make any judgements about the efficacy or effectiveness of bedaquiline when used for longer than 6 months; however, it did allow the GDG to determine that the safety profile of bedaquiline use for longer than 6 months is becoming clearer. The group concluded that bedaquiline can be safely used in patients beyond 6 months, if decided by the programme or treating clinician, and if appropriate schedules of baseline testing and monitoring are in place. In addition, the treating clinician should be aware of the use of other potentially QT-prolonging medications in any MDR/RR-TB regimen, and the comparatively long half-life of bedaquiline, which means that bedaquiline will remain in human tissue beyond the duration of its use. The half-life of bedaquiline is about 6 months, and the half-life of the *N*-monodesmethyl metabolite (M2) is about 5.5 months *(76)*.[38]

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[37] "Bacteriological response" refers to bacteriological conversion with no reversion; "bacteriological conversion" describes a situation in a patient with bacteriologically confirmed TB where at least two consecutive cultures (for DR-TB and drug-susceptible TB) or smears (for drug-susceptible TB only), taken on different occasions at least 7 days apart, are negative; and "bacteriological reversion" describes a situation where at least two consecutive cultures (for DR-TB and drug-susceptible TB) or smears (for drug-susceptible TB only), taken on different occasions at least 7 days apart, are positive either after the bacteriological conversion or in patients without bacteriological confirmation of TB. *(75)*

[38] This is the mean terminal half-life of bedaquiline and the M2 metabolite; this longer terminal elimination phase probably reflects the slow release of bedaquiline and M2 from peripheral tissues *(76)*.

Concurrent bedaquiline and delamanid use

The GDG 2019 felt that there was insufficient evidence to assess the efficacy or effectiveness of the concurrent use of bedaquiline and delamanid. However, the group concluded that the safety data assessed in 2019 suggest there are no additional safety concerns regarding the concurrent use of bedaquiline and delamanid. Therefore, bedaquiline and delamanid may be used in patients who have limited options for other treatment; that is, for patients with a small number of other effective drugs included in their regimen, probably due to an extensive drug-resistance profile or intolerance to other second-line TB medications. Appropriate schedules of safety monitoring (at baseline and throughout treatment) should be in place for these patients, including ECG and electrolyte monitoring, and clinicians should be cognizant of other medicines in the regimen that can either prolong the QT interval or cause other potential adverse events.

The 2021 WHO model list of essential medicines *(77)* includes all agents required for longer regimens.

Drug susceptibility testing

These guidelines stress past advice that a patient's MDR/RR-TB strain should be tested for susceptibility to medicines planned for inclusion in the regimen, so that effectiveness can be maximized. Access to rapid diagnostic testing would help clinicians to decide whether the patient is eligible for a specific MDR/RR-TB regimen, and what agents to include in a longer MDR-TB regimen. The recommendations on regimen design need to be accompanied by continued efforts to increase access to DST for medicines for which there are reliable methods, and by the development and roll-out of DST for the newer medicines. However, potentially life-saving treatment should not be withheld until all DST results become available, and empirical treatment with a regimen that is likely to be effective may need to be started, then adjusted once DST results become available.

An important observation in the 2018 IPD meta-analysis for longer regimens is that when a DST result indicates resistance to an agent, it is better to replace that agent. This also applies to medicines for which DST or the DST method used is known to be unreliable for clinical decision-making. Although DST is important for guiding effective treatment, DST results present uncertainties for several regimen components (e.g. cycloserine, streptomycin and ethambutol). "Likelihood of effectiveness" is generally assessed in the programmatic setting on the basis of one or more of the following: confirmed susceptibility in the individual patient, confirmed susceptibility in the presumed source case, no known resistance to another drug that has cross-resistance to the medicine, rare use of the medicine in an area (possibly supported by low drug-resistance levels from surveillance activities), and no previous use of the medicine in a regimen that failed to cure that same patient. When there is uncertainty about the effectiveness of a certain agent, that agent may still be included in the regimen, but it should not be considered as one of the target number of medicines needed; clinical judgement should be used to decide whether the benefit from its inclusion outweighs any added toxicity, pill burden or other disadvantages. The design of the regimen must consider the relative benefits and harms to the individual patient, including drug–drug interactions.

Dosage and duration

The guidelines update in 2018 revised the weight-based dosage schedules for medicines used in MDR-TB regimens for both children and adults (see the *Operational handbook on tuberculosis (3)*). The update to the dosages benefited from the expertise of the GDG members, and from an extensive consultation with other specialists in different fields. It was based on the latest knowledge available about the optimal use of the medicines involved *(78)*. Adherence to the schedules is advised as far as possible. Manipulation of tablets (e.g. splitting, crushing or dissolving in water) outside their indications is to be avoided because this may interfere with the bioavailability of the drugs.[39]

[39] This is particularly problematic with the delamanid tablet, the contents of which are most unpalatable (*see* summaries of unpublished data for the 2018 guidelines update in **Web Annex 5**).

It is important to prevent treatment interruption, to increase the likelihood of treatment success. One measure that can help to increase retention is supporting patient adherence, either by facilitating patient visits to health care facilities or home visits by health care staff, or by using digital technologies for daily communication *(37)*.

3.6 Monitoring and evaluation

Patients on longer MDR-TB treatment regimens need to be monitored for response to treatment and for safety, using reasonable schedules of relevant clinical and laboratory testing *(10, 39)*. The WHO framework for aDSM needs to be applied to patients on any type of MDR/RR-TB regimen, to ensure appropriate action and an acceptable level of monitoring for adverse events and prompt response to such events – alongside monitoring for treatment outcomes. Electrocardiography may be indicated as more regimens in the future may have two or three agents that are expected to prolong the QT interval. Audiometry and specific biochemical tests should also be made available whenever certain agents are included in the regimens. Treatment in pregnancy with postpartum surveillance for congenital anomalies will help to inform future recommendations for MDR/RR-TB treatment during pregnancy.

A separate recommendation on the use of culture and microscopy to monitor bacteriological response during treatment was made in the 2018 update of the guidelines (see **Section 5** regarding PICO question 11 MDR/RR-TB, 2018). Access to DST of medicines for which there are reliable methods and the development of other methods for newer medicines (e.g. sequencing) are critical (and in the case of DST, necessary) accompaniments to the treatment recommendations in these guidelines.

Patients on longer MDR-TB treatment regimens need to be monitored for treatment response and for safety, using reasonable schedules of relevant clinical and laboratory testing *(10, 39)*. Response to treatment and toxicity are monitored through regular history-taking, physical examination and chest radiography; special tests such as audiometry, visual acuity tests and electrocardiography; and laboratory monitoring. Using smear microscopy or culture to assess conversion of bacteriological status is an important way to assess response, and most patients are expected to have converted to a sputum-negative status within the first few months of starting treatment. Persistence of culture positivity beyond that point, or close to the expected end of the intensive phase when injectable agents are in use, should trigger a review of the regimen and performance of DST. NTPs should also aim for complete registration of patients with MDR/RR-TB, through follow-up and monitoring of treatment outcomes as part of national surveillance. Regular review of MDR/RR-TB cohort data is essential.

Frameworks for the surveillance of bacteriological status, drug resistance and assignment of outcomes have been standardized in recent years *(79)*. In contrast, systematic monitoring of adverse events during and after the end of treatment needs to be strengthened in most NTPs, given the relative novelty of active pharmacovigilance within NTPs *(39, 54)*. The rationale for aDSM is largely supported by the increasing use worldwide of combinations of new and repurposed medications in MDR/RR-TB treatment regimens. The toxicity of certain agents may increase with the duration of use (e.g. nerve damage with linezolid), and may limit their continued use in a patient, sometimes resulting in complete cessation of treatment. The prospective collection of accurate data for key variables at the case-based level, using an electronic register, is strongly advised in the best interests of the individual patient, and to inform revisions of local and global policies *(80)*.

Section 4. Regimen for rifampicin-susceptible, isoniazid-resistant TB (Hr-TB)

4.1 Recommendations

No.	Recommendation
4.1	In patients with confirmed rifampicin-susceptible, isoniazid-resistant tuberculosis , treatment with rifampicin, ethambutol, pyrazinamide and levofloxacin is recommended for a duration of 6 months. *(Conditional recommendation, very low certainty of evidence)*
4.2	In patients with confirmed rifampicin-susceptible, isoniazid-resistant tuberculosis, it is not recommended to add streptomycin or other injectable agents to the treatment regimen. *(Conditional recommendation, very low certainty of evidence)*

4.2 Justification and evidence

The recommendations in this section address one PICO question:

> ***PICO question*** *(Hr-TB, 2018): In patients with isoniazid-resistant TB (other than MDR-TB), which treatment regimen composition and duration, when compared with 6 months or more of rifampicin–pyrazinamide–ethambutol, leads to a higher likelihood of success with least possible risk of harm?*

Treatment with rifampicin, ethambutol and pyrazinamide – with or without isoniazid – has been used for the treatment of patients with rifampicin-susceptible, isoniazid-resistant TB (Hr-TB) *(81–83)*. The evidence reviewed for this guideline compared treatment regimens with isoniazid, rifampicin, ethambutol, pyrazinamide ((H)REZ)[40] of different durations (e.g. 6-month regimens versus longer duration ones). Additionally, the review of evidence focused on determining whether treatment outcomes in Hr-TB patients receiving (H)REZ treatment regimens of variable duration could be improved with the addition of a fluoroquinolone or streptomycin.

The evidence used to determine the composition and duration of regimens relied primarily on an analysis of IPD that comprised 33 databases with an analysable population of 5 418 Hr-TB patients. All data used to develop these recommendations were derived from observational studies conducted in various settings (33% in Europe, 31% in the Americas, 26% in Asia and 6% in Africa) *(84)*.[41] In the IPD analysed, patient treatment regimens contained rifampicin, ethambutol, pyrazinamide, streptomycin, isoniazid and fluoroquinolones; thus, recommendations could be made only for regimens containing these anti-TB agents. Based on an assessment of the certainty of the evidence, carried out using predefined criteria, the certainty of the evidence was rated as very low.

Duration of (H)REZ

The analysis comparing (H)REZ treatment regimens for 6 months (6(H)REZ) and more than 6 months (>6(H)REZ) demonstrated that a 6(H)REZ regimen had a higher likelihood of treatment success than a >6(H)REZ regimen. Further analyses determined that there was no statistically significant difference in the treatment outcomes of patients receiving regimens of 6-month REZ (6REZ) and those receiving more than 6 months REZ (>6REZ). Data on intermittent dosing of the 6(H)REZ

[40] "(H)" indicates that isoniazid is optional.

[41] The number of patients highlighted in this section refers to the sample size of each study. However, the analysable sample size was later modified, depending on the availability of IPD for each analysable outcome (success and mortality).

and >6(H)REZ regimens were not included; hence, no inferences could be drawn about the use of alternating versus daily regimens. The effect of length of pyrazinamide use in the (H)REZ regimen was assessed, to investigate whether the use of this medicine could be minimized to the shortest possible duration. The reduction in treatment with pyrazinamide to less than 3 months was associated with a worse treatment outcome, even with the addition of streptomycin (aOR: 0.4, 95% CL: 0.2–0.7). In 118 patients on fluoroquinolone-containing regimens who received pyrazinamide for less than 4 months, the odds of treatment success were higher than in those who received a 6(H)REZ regimen, although the difference was not statistically significant.

Duration of levofloxacin use

In a subsample of 241 patients on an (H)REZ plus fluoroquinolone regimen, the median duration of fluoroquinolone use was 6.1 months (IQR: 3.5, 8.4), and for REZ it was 9 months (IQR: 7, 11). Hence, in the observational studies that informed the IPD, it seems that treatment length was based on the completion of 6 months of treatment with a fluoroquinolone.

Acquisition of drug resistance

The analysis suggested that amplification of resistance to rifampicin was lower in patients receiving the 6(H)REZ regimen (0.6%) than in those receiving >6(H)REZ (4.3%). This observation could be due to the selection and allocation of patients into specific regimens; for instance, the number of patients with extensive disease was slightly larger in those receiving >6(H)REZ. However, overall, the number of observations for each comparison was small and the effect was not statistically significant (aOR, 0.2, 95% CL: 0.02–1.70).

Adverse events

Data on adverse events were not evaluated owing to a lack of standardization (dissimilar reporting). The GDG also considered two reports containing data from patients from the United States of America (USA) in whom a detailed assessment of adverse events suggested a risk of excess hepatotoxicity with the 6(H)REZ combination *(85)*. Drug-induced hepatotoxicity is not uncommon with anti-TB drugs. It has also been reported in individuals receiving rifampicin and pyrazinamide for 2 months for the treatment of TB infection – in such individuals, a much higher occurrence of hepatotoxicity has been observed than in those receiving only isoniazid preventive therapy *(86)*. It is not known whether the risk of hepatotoxicity differs between 6REZ and 6HREZ.

Addition of a fluoroquinolone

In patients with Hr-TB, treatment success rates were higher when fluoroquinolones were added to (H)REZ regimens than when patients were treated with 6(H)REZ or >6(H)REZ, without the addition of fluoroquinolones (aOR: 2.8, 95% CL: 1.1–7.3). With the addition of fluoroquinolones in patients receiving (H)REZ, the number of deaths was reduced (aOR: 0.4, 95% CL: 0.2–1.1). Acquisition of additional resistance with progression to MDR-TB was also reduced when fluoroquinolones were added to a ≥6(H)REZ regimen (aOR: 0.10, 95% CL: 0.01–1.2), albeit with small absolute numbers; 0.5% (1/221) of patients on ≥6(H)REZ plus fluoroquinolones acquired resistance to rifampicin compared with 3.8% (44/1 160) of patients who did not receive fluoroquinolones. Residual confounding could have increased this observed effect. The directness of the evidence was therefore downgraded because it was unclear whether fluoroquinolones were used at the beginning of treatment or only once DST results were available (in the second month or later).

Addition of streptomycin

The analysis showed that the addition of streptomycin (up to 3 months) to an (H)REZ regimen with less than 4 months of pyrazinamide decreased the likelihood of treatment success (aOR: 0.4, 95% CL:

0.2–0.7), an effect that may in part be due to confounding. Addition of streptomycin did not reduce mortality significantly (see **Web Annex 3** and **Web Annex 4**). There were no data on the use of other injectable agents (i.e. kanamycin, amikacin and capreomycin) for the treatment of Hr-TB.

Treatment outcomes

When analysing the overall treatment outcomes for each one of the regimens assessed for this review, other limitations related to the characteristics of patients included in these studies were evident and could not be controlled for. Those limitations were patient selection, and allocation to treatment with specific regimens and their relationship with disease severity. Outcomes appeared to be worse in patients with cavitary disease, persistence of sputum smear positivity and previous history of TB treatment, who received a 6(H)REZ or >6(H)REZ regimen with an additional 3 months of pyrazinamide and 1–3 months of streptomycin (see Hr-TB, 2018 in **Web Annex 3**). However, the limited number of observations made it difficult to draw definitive conclusions based on the severity of TB disease or the effect of other comorbidities on this regimen.

In formulating the recommendations, the GDG assessed the overall balance between benefits and harms of an (H)REZ–levofloxacin regimen; they also considered values and preferences (paying special attention to considerations of equity, acceptability and feasibility), in addition to clinical outcomes and the potential risks of increasing toxicities (see **Web Annex 3** and **Web Annex 4** for details). The conclusions of the GDG were that a regimen composed of 6 months of REZ plus fluoroquinolones was associated with higher treatment success rates (with or without the addition of isoniazid). The difference between the 6(H)REZ and >6(H)REZ regimens was modest, slightly favouring the 6-month regimen (not statistically significant). The GDG acknowledged that it was not possible to control for all possible confounding by indication when comparing the 6(H)REZ and >6(H)REZ regimens. As an example, although data on the extent of disease were not systematically captured for all patients, it is possible that a larger number of cases with extensive disease received >6(H)REZ regimens, resulting in poor outcomes for this group of patients (given the extent of disease) and possibly favouring the 6(H)REZ regimen.

The GDG acknowledged the safety implications of (H)REZ–levofloxacin, particularly the hepatotoxicity associated with prolonged use of pyrazinamide-containing multidrug regimens. However, reducing the duration of the treatment with pyrazinamide to 3 months or less was associated with worse treatment outcomes, at least in Hr-TB regimens without a fluoroquinolone. Furthermore, the use of streptomycin in these regimens was associated with no significant added benefit. The use of streptomycin and other injectable agents has also been associated with increased serious adverse events *(87–89)*. On this basis, the GDG agreed that current data supported the use of the (H)REZ–levofloxacin regimen without streptomycin or any other injectable agent in Hr-TB cases, unless there is a compelling reason to use these agents (e.g. certain forms of polydrug resistance).

The GDG also noted that patients were likely to place a high value on a 6-month regimen, the likelihood of a relapse-free successful outcome and, especially, the implementation of a regimen without the use of injectable agents. GDG members agreed that the use of the 6(H)REZ regimen would probably increase health equity, given that the cost of the components is relatively low (compared with the recommended regimens for MDR/RR-TB) and the increased probability of cure in a substantial number of patients. In addition, the exclusion of streptomycin and other injectable agents reduces potential barriers to regimen administration.

Although patient costs were not factored into the analysis, the GDG agreed that improving diagnostic capacity to detect isoniazid resistance would be beneficial. A modelling analysis performed for the 2011 update of the WHO *Guidelines for the programmatic management of drug-resistant tuberculosis (8)* estimated that the best strategy for averting deaths and preventing acquired MDR-TB was to undertake DST in all patients before treatment, using a rapid test that detects resistance to isoniazid and rifampicin *(90)*. The modelling work also showed that rapid testing for resistance to both isoniazid and rifampicin at the time of diagnosis was the most cost-effective testing strategy for any patient

group or setting, even at very low levels of resistance among TB patients (MDR-TB in >1% and isoniazid resistance [other than MDR-TB] in >2%).

In general, the GDG considered that the use of the 6(H)REZ–levofloxacin regimen would be feasible in most DR-TB treatment settings, and that the use of a regimen based on medicines that are administered orally may increase feasibility. Altogether, based on present evidence, when discussing the balance between benefits and harms, preferences and values for patients and other end-users, the GDG reached overall agreement on the beneficial effect that the Hr-TB regimen may have, if used in conformity with these policy recommendations. Although there was no clear evidence to suggest that the addition of isoniazid to this regimen would be beneficial, the four-drug (H)REZ fixed-dose combination (FDC) may be more convenient for the patient and the health service because it removes the need to use single drugs.

Consistent with the overall framework for the management and care of patients diagnosed with DR-TB, careful selection of patients is a fundamental principle. Ahead of starting the (H)REZ–levofloxacin regimen, it is essential that resistance to rifampicin be excluded, using WHO-recommended genotypic or phenotypic methods *(91, 92)*. Ideally, resistance to fluoroquinolones (and, if possible, to pyrazinamide) should be similarly excluded before treatment, to help avert the acquisition of additional drug resistance (see **Section 4.4**).

Empirical treatment of Hr-TB is generally not advised. In cases where a diagnosis of Hr-TB is strongly presumed (e.g. close contacts of Hr-TB cases with active TB but without laboratory confirmation of Hr-TB), (H)REZ–levofloxacin may be introduced pending laboratory confirmation of isoniazid resistance, provided that rifampicin resistance has been reliably excluded. Should DST results eventually indicate susceptibility to isoniazid, levofloxacin is stopped, and the patient completes a 2HREZ/4HR regimen (i.e. 2 months of HREZ followed by 4 months of HR). For patients in whom Hr-TB is detected after the start of treatment with the 2HREZ/4HR regimen, the (H)REZ component drugs are continued (or pyrazinamide and ethambutol are reintroduced) and levofloxacin added, once rifampicin resistance has been excluded.

The duration of an (H)REZ–levofloxacin regimen is usually determined by the need to complete 6 months of a levofloxacin-containing regimen. Thus, in cases where the diagnosis of Hr-TB is made after first-line TB treatment has already been initiated, the patient may receive more than 6 months of (H)REZ by the end of treatment. When the confirmation of isoniazid resistance arrives late into treatment with a 2HREZ/4HR regimen (e.g. 5 months after start during the continuation phase), the clinician would need to decide, based on an assessment of the patient's condition, whether a 6-month course of (H)REZ–levofloxacin needs to be started at that point or not.

The addition of levofloxacin to (H)REZ is recommended in all patients with Hr-TB, with the exception of the following situations: resistance to rifampicin cannot be excluded; known or suspected resistance to levofloxacin; known intolerance to fluoroquinolones; known or suspected risk for prolonged QT interval; and pregnancy or during breastfeeding (not an absolute contraindication). In a patient with Hr-TB in whom a fluoroquinolone cannot be used, the patient may still be treated with 6(H)REZ.

When additional resistance (especially to pyrazinamide) is suspected or confirmed, appropriate treatment regimens will have to be designed individually. The data reviewed for this guideline could not provide separate evidence-based recommendations for such cases.

Where possible, isoniazid resistance testing should also include information on the specific mutations associated with resistance to isoniazid (*kat*G or *inh*A). In addition, knowledge about overall host acetylator[42] status at country or regional level will be useful, given that these may have implications for regimen design *(93)*.

[42] Decreased efficacy and toxicity of isoniazid have been related to its increased metabolism (acetylation) in certain individuals, as determined by mutations in the *N*-acetyltransferase type 2 (NAT2) gene.

Automated, cartridge-based and high-throughput diagnostic platforms are available (as an alternative to LPA) and countries have the capacity to use them. These platforms can, simultaneously or in separate tests, detect TB, and resistance to rifampicin, fluoroquinolones and isoniazid.

4.3 Subgroup considerations

Children

In the IPD review, only 2% of Hr-TB patients were children; thus, a separate estimate of effect for paediatric patients was not possible. However, there is no reason why the results and recommendations cannot be extrapolated from adults to children, considering that the regimen components have been standard paediatric TB medicines for many years.

Patients with extensive disease

Although the IPD analysis did not provide evidence for duration of treatment extension, the prolongation of the 6(H)REZ–levofloxacin regimen to more than 6 months could be considered on an individual basis for patients with extensive disease *(94)*. Prolongation of treatment may increase the risk of adverse events in some cases (see **Section 1.5**).

People living with HIV

The effect of longer duration TB treatment among PLHIV with and without ART has been studied among patients with drug-susceptible TB *(95)*. In these cases, relapse has been reported to be 2.4 times higher in PLHIV who were not on ART and who received 6 months of treatment than in patients in whom treatment was prolonged (up to 9 months). In patients with drug-susceptible TB initiated on ART, no significant benefit from prolonging rifampicin-containing regimens for over 6 months has been observed *(37)*. In the current analysis, only a limited number of patients received ART; nonetheless, in TB patients with HIV coinfection, the first priority is to ensure that they are started on ART within 8 weeks of TB treatment initiation (regardless of CD4 count), in accordance with WHO guidelines *(96)*. The 6(H)REZ–levofloxacin regimen is therefore recommended in PLHIV.

Extrapulmonary disease

No data were available for patients with exclusive extrapulmonary Hr-TB. The regimen composition proposed is likely to be effective even in these patients. However, the treatment of patients with extrapulmonary TB should be designed in close consultation with appropriate specialists (e.g. infectious disease physicians and neurologists), to decide upon individual variations in treatment duration and supportive care, as needed.

4.4 Implementation considerations

Case scenarios

Implementing these recommendations requires the (H)REZ–levofloxacin regimen to be administered only in patients in whom resistance to isoniazid has been confirmed and resistance to rifampicin has been excluded. Preferably, testing for resistance to fluoroquinolones (and, if possible, to pyrazinamide) is also done before starting treatment. It is envisaged that the treatment regimen for Hr-TB will apply in the following situations:

- *Hr-TB and rifampicin susceptibility are confirmed before TB treatment is started.* Treatment with (H)REZ–levofloxacin is started immediately. If the diagnosis is strongly presumed (e.g. close contacts of a confirmed Hr-TB source case) but results of DST are still pending, the regimen may be

introduced. If the DST results taken at the start eventually show susceptibility to isoniazid, then levofloxacin is stopped, and the patient continues treatment to complete a 2HREZ/4HR regimen.

- *Hr-TB is confirmed after the start of treatment with the 2HREZ/4HR regimen.* This includes patients who had undiagnosed isoniazid resistance initially or who developed isoniazid resistance later while on treatment with a first-line regimen. In such cases, rapid molecular testing for rifampicin resistance must be done (or repeated). Once rifampicin resistance has been excluded, a full 6-month course of (H)REZ–levofloxacin is given. The duration is driven by the need to give levofloxacin for 6 months, which usually implies that the companion first-line medicines are taken for longer than this.

If rifampicin resistance is detected, the patient needs to be started on a recommended MDR-TB treatment regimen, as described in other sections of these guidelines.

Diagnostic capabilities

The overall aim of TB treatment is to achieve cure without relapse in all patients, interrupting *M. tuberculosis* transmission and preventing the acquisition (or amplification) of additional drug resistance. Globally, Hr-TB is more prevalent than MDR-TB. Thus, all countries need to move towards universal testing of both isoniazid and rifampicin resistance at the start of TB treatment, and to ensuring careful selection of patients eligible for the (H)REZ–levofloxacin regimen.[43] The minimum diagnostic capacity to appropriately implement these recommendations is rapid molecular testing for rifampicin resistance before the start of treatment with the Hr-TB regimen and, preferably, the ruling out of fluoroquinolone resistance using WHO-recommended tests.

Rapid molecular tests such as Xpert MTB/RIF, Xpert MTB/XDR and LPAs are preferred, to guide patient selection for the (H)REZ–levofloxacin regimen *(92, 97)*.

Surveillance of DR-TB indicates that fluoroquinolone resistance among patients with rifampicin-susceptible TB is generally low worldwide *(98)*. However, national data on the prevalence of fluoroquinolone resistance – including targeted or whole-genome sequencing to detect specific mutations associated with resistance to fluoroquinolones *(52)* – could help to guide testing policies when countries implement the Hr-TB treatment recommendations.

When additional resistance (e.g. to both fluoroquinolones and pyrazinamide) is suspected or confirmed, treatment regimens that include other second-line TB medicines may have to be designed individually. The current review could not provide further evidence on effective regimens in patients with polyresistant disease.

Support and close monitoring of patients are needed to maximize treatment adherence and enable early detection of patients who are not responding to treatment (e.g. those with persistent sputum culture or smear positivity). In the presence of non-response to treatment, DST for rifampicin and the fluoroquinolones should be repeated, preferably with Xpert MTB/XDR or LPA. Documented acquisition of resistance to rifampicin or a fluoroquinolone while on the Hr-TB treatment regimen should alert the clinician to the need to review the entire clinical and microbiological status of the patient, and change the regimen where necessary.

Levofloxacin is proposed as the fluoroquinolone of first choice in the Hr-TB treatment regimen for several reasons. First, the safety profile of this medicine is better characterized than that of other fluoroquinolones, and levofloxacin was the fluoroquinolone most frequently used in the studies reviewed for this guidance. Second, in comparison to moxifloxacin, levofloxacin has fewer known drug interactions with other medications. For example, although both plasma peak concentration and exposure to moxifloxacin decrease significantly when the drug is combined with rifampicin *(99)*, the same effect has not been reported for levofloxacin, possibly because levofloxacin undergoes limited metabolism in humans and is excreted unchanged in the urine *(100)*. Third, although levofloxacin

[43] The association between previous TB treatment history and Hr-TB is less strong than the association in MDR-TB. As a result, previous TB treatment is less reliable as a proxy for Hr-TB and a laboratory diagnosis is therefore important.

may interfere with lamivudine clearance, in contrast to moxifloxacin, there are no contraindications for its use with other antiretroviral agents *(36)*.

The addition of levofloxacin to (H)REZ is recommended in patients with Hr-TB, with the exception of the following situations:

- resistance to rifampicin cannot be excluded (i.e. unknown susceptibility to rifampicin, or indeterminate or error results on Xpert MTB/XDR);
- known or suspected resistance to levofloxacin;
- known intolerance to fluoroquinolones;
- known or suspected risk for prolonged QT interval; and[44]
- if possible, in pregnancy or during breastfeeding (not an absolute contraindication).

Sometimes, the confirmation of isoniazid resistance arrives late (e.g. 5 months into a 2HREZ/4HR regimen). In such cases, a decision to start 6 months of (H)REZ–levofloxacin depends on the patient's clinical condition and microbiological status.

If levofloxacin cannot be used because of toxicity or resistance, the patient may be given 6(H)REZ as an alternative. Based on the results of the evidence review for these guidelines, replacement of levofloxacin with an injectable agent is NOT advised. The evidence review could not inform on the effect of other second-line TB medicines on treatment effectiveness.

Addition of isoniazid

There was no clear evidence that the addition of isoniazid affects patients (i.e. adding benefit or harm). For patient convenience and ease of administration, the four-drug HREZ FDCs[45] may be used to deliver the Hr-TB treatment regimen alongside levofloxacin.

The use of high-dose isoniazid (10–15 mg/kg per day in adults) was not evaluated in this review owing to insufficient data. However, the GDG discussed the effect of increasing isoniazid dosing beyond that provided in weight-banded FDCs, depending on the type of molecular mutations identified. In vitro evidence suggests that when specific *inh*A mutations are detected (and when *kat*G mutations are absent), increasing the dose of isoniazid is likely to be effective; thus, additional isoniazid up to a maximum dose of 15 mg/kg per day could be considered. In the case of *kat*G mutations, which usually confer a higher level resistance, the use of isoniazid even at a higher dose is less likely to be effective *(101)*.[46]

Dosage

Although the IPD analysis did not provide evidence to address the frequency of dosing, it is best to avoid intermittent or divided dosing of the 6(H)REZ–levofloxacin regimen *(37, 102, 103)*. In the absence of full information about optimal drug doses, a weight-band dosing scheme for levofloxacin is recommended.[47]

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[44] Baseline-corrected QT. Prolongation of the QT interval and isolated cases of *torsades de pointes* have been reported. Avoid use in patients with known prolongation, those with hypokalaemia, and with other drugs that prolong the QT interval.

[45] Although most countries currently procure the four-drug FDC via the Stop TB Partnership's GDF, in settings where only the three-drug combination FDC (i.e. HRZ) is available, ethambutol has to be administered separately.

[46] An isolated *kat*G or *inh*A mutation can correspond to variable MIC levels. This implies that *inh*A mutations do not always indicate low-level isoniazid resistance, and that *kat*G mutations are not necessarily correlated with high-level isoniazid resistance. However, the presence of both mutations is usually an indication of high-level resistance *(101)*.

[47] Studies included in this IPD analysis involved the use of regimens containing levofloxacin (usually at a dose of 750–1 000 mg/day), moxifloxacin (400 mg/day) or gatifloxacin (400 mg/day), as well as early-generation fluoroquinolones (ciprofloxacin and ofloxacin), which are no longer recommended for the treatment of DR-TB. Gatifloxacin is currently unavailable in quality-assured formulations, and ciprofloxacin and ofloxacin are no longer recommended for use in DR-TB care.

Drug–drug interactions

Levofloxacin may interfere with lamivudine clearance (increasing the levels of lamivudine) but it is not contraindicated with other antiretroviral agents, and no drug dosing adjustments are needed *(36)*. Co-administration of levofloxacin with oral divalent cation-containing compounds (e.g. antacids) may impair its absorption and should be avoided *(10)*. Restriction of concomitant use of milk products is not necessary.

Treatment prolongation beyond 6 months

Prolonging of treatment beyond 6 months may be considered for patients with extensive disease or in those slow to convert to smear or culture negative. In the latter, acquisition of additional resistance to rifampicin must be ruled out, as must resistance to fluoroquinolones and pyrazinamide, if possible. Such patients require careful monitoring and follow-up.

Cost

A cost–effectiveness analysis was not performed for this review. **Table 4.1** presents approximate prices for a full course of medicines with the different regimens in adults, based on the cost of products available from the GDF *(45)*. Use of FDCs, even for part of the regimen, reduces costs. Medicines needed for a 6HREZ–levofloxacin regimen cost about three times as much as a 2HREZ/4HR regimen when using the HREZ FDC. The treatment of Hr-TB according to these guidelines is not expected to significantly increase operational costs.

Table 4.1. Illustrative costs of regimens used to treat Hr-TB compared with the 6-month first-line TB regimen

Regimen	Average weighted prices, US$[a]
2HREZ/4HR	36
6HREZ	55
6REZ–Lfx	99
6HREZ–Lfx	76
9HREZ–Lfx	113

FDC: fixed-dose combination; HR: isoniazid and rifampicin; HREZ: isoniazid, rifampicin, ethambutol and pyrazinamide; Hr-TB: rifampicin-susceptible, isoniazid-resistant; Lfx: levofloxacin; REZ: rifampicin, ethambutol and pyrazinamide; TB: tuberculosis.

[a] Prices are as of 15 March 2020 for a 60 kg adult, and they reflect the use of FDCs whenever possible. Average weighted prices are based on prospective market share allocation and are indicative only. For budgeting purposes, it is recommended to use the budgeting prices from the Stop TB Partnership *(45)*.

Source: Stop TB Partnership (2020) *(45)*.

Adherence

The IPD analysis contained limited data on the treatment adherence strategies used, such as directly observed treatment and self-administered therapy (SAT). Improved treatment success rates appeared to be associated with increased patient support, including medication adherence support (e.g. by means of digital technologies) or other means, as recommended by WHO *(37)*. In contrast to regimens for drug-susceptible TB and MDR-TB, the recommended Hr-TB treatment regimen does not have an intensive phase and a continuation phase, simplifying the delivery and monitoring of treatment.

4.5 Monitoring and evaluation

Patients who receive the (H)REZ–levofloxacin regimen need to be monitored during treatment, using schedules of clinical and laboratory testing. The definitions to use when assigning outcomes are the same as those used for drug-susceptible TB *(79)*. Signs of non-response or treatment failure should be followed up with DST for rifampicin resistance and, if possible, for fluoroquinolones and pyrazinamide. To limit the risk of acquisition of additional resistance, the addition of single TB medicines should be avoided in patients who remain smear positive or culture positive after month 2 of treatment, those who do not show a favourable clinical response and those without recent DST results.

As with any other TB medicine and regimen, safety precautions are required to ensure the rapid identification and proper management of any serious adverse event. Close clinical monitoring is essential for all patients receiving this regimen, particularly liver function tests, given the hepatotoxic potential of prolonged pyrazinamide use. If possible, all patients should be tested each month for levels of AST (also known as serum glutamic oxaloacetic transaminase, SGOT). If resources are not available to monitor all patients on the Hr-TB treatment regimen, monthly monitoring of patients at high risk (e.g. patients coinfected with viral hepatitis or with a history of heavy alcohol use) is strongly advised. Additionally, to prevent and manage the potential toxic effects of ethambutol in children (e.g. retrobulbar neuritis), it is necessary to adhere to the correct doses recommended for paediatric populations. Early signs of ethambutol toxicity can be tested in older children through red–green colour discrimination. Monitoring for retrobulbar neuritis can be undertaken early when appropriate *(104)*.

Section 5. Monitoring patient response to MDR/RR-TB treatment using culture

5.1 Recommendation

No.	Recommendation
5.1	In multidrug- or rifampicin-resistant tuberculosis (MDR/RR-TB) patients on longer regimens, the performance of sputum culture in addition to sputum smear microscopy is recommended to monitor treatment response. *(Strong recommendation, moderate certainty in the estimates of test accuracy)* It is desirable for sputum culture to be repeated at monthly intervals.

5.2 Justification and evidence

The recommendation in this section addresses the following PICO question:

PICO question *(MDR/RR-TB, 2018). In patients with MDR/RR-TB treated with longer or shorter regimens composed in accordance with WHO guidelines, is monitoring using monthly cultures, in addition to smear microscopy, more likely to detect non-response to treatment?*

Previous studies have indicated that monthly culture is the optimum strategy to detect non-response as early as possible and was conditionally recommended by WHO in 2011 as the preferred approach *(8, 105, 106)*. The findings of the evidence review and analysis performed for this question are expected to influence the continued validity, in its present form, of the 2011 WHO recommendation *(8)*. Since then, significant changes in MDR-TB treatment practices have taken place on a large scale globally, such as the wider use of later-generation fluoroquinolones, bedaquiline and linezolid; a tendency towards an intensive phase of longer duration; and the widespread use of the shorter regimen, which

could influence the speed and durability of culture conversion during the continuation phase, when this PICO question is of greatest relevance.

Achieving sustained bacteriological conversion from positive to negative is widely used to assess response to treatment in both drug-susceptible TB and DR-TB. Culture is a more sensitive test for bacteriological confirmation of TB than direct microscopy of sputum and other biological specimens. Culture also facilitates phenotypic testing for DST, a critical consideration in TB diagnostics. However, performing culture requires considerable logistical organization and a well-equipped laboratory to limit cross-contamination, ensure proper bacterial growth and match other quality standards. Apart from the resource requirements, culture results become available after a significant delay of weeks or months, contrasting markedly with the relative immediacy of the result of direct microscopy (although microscopy cannot confirm mycobacterial viability). Although molecular techniques can now provide a rapid and reliable diagnosis, they cannot replace culture or microscopy for the monitoring of bacteriological status during treatment.

The evidence used to explore the added value of culture over sputum smear microscopy alone, and the optimal frequency of monitoring, was obtained from a subset of the IPD reported to WHO by South Africa for the 2018 update. These observational data from South Africa comprised 26 522 patients overall. Of these, 22 760 records were excluded from the dataset for the following reasons: 11 236 had a treatment outcome of death or loss to follow-up; 698 had a successful treatment outcome but had received less than 17.5 months of treatment; 1 357 had fewer than six culture samples recorded; 1 632 had no baseline culture recorded; 2 502 were baseline culture negative; 2 920 were smear negative at baseline or had a missing smear at baseline; and 2 415 had insufficient smear data to match the culture data. This left 3 762 MDR/RR-TB patients (with 1.8% being children; i.e. aged <15 years) treated with longer MDR-TB regimens between 2010 and 2015, who had both monthly smear and culture data throughout treatment to address PICO question 11 (MDR/RR-TB, 2018). About 60% of these patients were PLHIV. The analysis focused on whether monthly culture versus monthly smear microscopy or culture every 2 months is needed to not miss treatment failure in MDR/RR-TB patients on treatment. The odds of treatment failure in patients who do not convert at 6 months or later was also discussed (see **Section 5.4** and **Table 5.1**). The data could not address the outcome on acquisition (amplification) of additional drug resistance, nor could it assess directly whether the frequency of culture or smear microscopy had an identical effect on failure in patients on the 9–12-month shorter MDR-TB regimen, as envisaged in the original PICO question 11 (MDR/RR-TB, 2018). Based on an assessment of the certainty of the evidence, carried out using predefined criteria and documented in GRADEpro, the test accuracy certainty of the evidence was rated as moderate.

The IPD meta-analysis compared the performance of the two methods in terms of sensitivity and specificity, and culture testing once a month compared with once every 2 months (to assess the minimum frequency of testing needed to not unnecessarily delay any revision of the treatment). The focus of the analysis was to compare how the two tests performed in terms of predicting treatment failure or relapse.

The main findings of the analysis were that monthly culture had a higher sensitivity than monthly smear microscopy (0.93 vs 0.51) but slightly lower specificity (0.97 vs 0.99). Likewise, the sensitivity of culture done every month was much higher than once every 2 months (0.93 vs 0.73) but had a slightly lower specificity (0.97 vs 0.98). Monthly culture increased the number of patients detected with a true positive bacteriological result by 13 per 1 000 patients and reduced false negative results by 13 per 1 000 patients when compared with sputum smear microscopy alone. In contrast, monthly culture was estimated to lead to 17 per 1 000 fewer true negative results and 17 per 1 000 more false positive results for treatment failure, implying that treatment may be prolonged in the case of false positivity or missed true negativity. The added inconvenience to the patient and programme is considered relatively small, given that taking sputum and many other biological specimens is usually non-invasive and routine practice in many programmes. In a setting where testing is repeated at monthly intervals, a single false positive test result is unlikely to prove harmful to the patient because

treatment decisions usually rely upon at least two consecutive positive results (to denote prolonged positivity or reversion) and the effect of one spurious result would last only until the test repeated 1 month later is reported.

The crude odds of treatment failure increased steadily with each additional month without bacteriological conversion, from 3.6 at the end of the first month to 45 at the eighth month when using culture (**Table 5.1**). However, no discrete cut-off point (to serve as a reliable marker of a failing regimen) could be discerned at which the odds of failure increased sharply when monitoring with either sputum smear microscopy or culture. The threshold for when to change treatment thus depends on the clinician's desire to minimize the risk of failure and, in particular, to limit the risk of prolonging a failing regimen.

Table 5.1. Crude odds ratios (95% CLs) of treatment failure in MDR/RR-TB patients without sputum conversion by the end of successive months of treatment compared with patients who converted, by testing method used; IPD meta-analysis for PICO question 7 MDR/RR-TB, 2018 (South Africa, *n*=3 762)

Crude odds ratios according to	Month							
	1	2	3	4	5	6	7	8
Culture	**3.6**	**4.1**	**5.2**	**7.4**	**10.3**	**16.4**	**24.7**	**44.5**
	(2.11, 5.97)	(2.76, 6.09)	(3.55, 7.55)	(5.00, 10.80)	(6.88, 15.38)	(10.72, 25.00)	(15.53, 39.20)	(26.53, 74.46)
Smear microscopy	**1.9**	**2.7**	**3.2**	**4.2**	**6.8**	**10.4**	**16.5**	**28.9**
	(1.27, 2.73)	(1.82, 3.88)	(2.11, 4.73)	(2.69, 6.48)	(4.19, 10.97)	(6.00, 17.92)	(9.15, 29.77)	(14.87, 56.14)

CL: confidence limits; IPD: individual patient data; MDR/RR-TB: multidrug-resistant or rifampicin-resistant tuberculosis; PICO: population, intervention, comparator and outcome.

There was moderate certainty in the estimates of test accuracy and the GDG considered that, under normal conditions, culture would always be a more sensitive test of positive bacterial status than sputum smear microscopy. However, the overall quality of the evidence was judged to be low. The effects observed may vary in patients or populations with a profile markedly different from the one included in the analysis, such as low HIV-prevalence settings, children, patients with extrapulmonary forms of disease or those treated with the shorter MDR-TB regimen. The 3 762 patients included in the analysis had similar clinical characteristics to the 22 760 individuals excluded, although they were slightly less likely to be HIV coinfected, have a history of previous treatment or have second-line drug resistance. Conversely, the rate of failure in those included in the analysis was only 3% compared with 12.7% of those excluded from the analysis.

5.3 Subgroup considerations

The recommendation would apply to any longer regimen, regardless of the number of Group A, B or C agents used and whether an injectable (intensive) phase was used or not. The GDG considered that the findings may apply to other key patient subgroups.

Patients aged below 15 years with MDR/RR-TB

Patients aged below 15 years with MDR/RR-TB comprised less than 2% of the IPD meta-analysis analysed for PICO question 11 (MDR/RR-TB, 2018). Younger children usually cannot produce sufficient sputum spontaneously to allow a bacteriological diagnosis (many are typically sputum smear microscopy negative). In these patients, culture may be a more sensitive way to detect viable TB bacilli even if very few organisms are present in the sputum or other samples that are below the detection threshold of direct microscopy. However, in children who are unable to expectorate, gastric aspirates or induced sputa may be possible, but the repetition of such tests at monthly frequency may not be acceptable.

Extrapulmonary disease

Extrapulmonary disease is commonly paucibacillary; therefore, biological specimens may contain few or no bacilli. In such situations, detection of persistent disease is more likely with culture, although collection of samples often poses problems. Direct microscopy should still be attempted because it may determine positivity much faster than culture.

HIV-negative individuals

HIV-negative individuals with TB typically have higher bacterial counts in the sputum and a greater likelihood of detection with smear microscopy. In such a situation, it might be expected that the difference in test sensitivity between smear and culture would be less extreme, because fewer patients would have subthreshold bacterial counts. However, past studies on datasets from multiple sites in which HIV positivity was low reported findings that led to the WHO recommendation, even in 2011, for joint use of both microscopy and culture, preferably every month.

Patients on the shorter MDR-TB regimen

Patients on the shorter MDR-TB regimen have a much shorter duration of intensive phase and total treatment. They receive seven drugs in the initial phase and, if fully compliant with the inclusion and exclusion criteria, usually have a more favourable prognostic outlook than other MDR-TB patients. Programmes may thus consider that patients on a shorter MDR-TB regimen may need less frequent or no culture to monitor treatment. Although the current analysis did not include patients treated with shorter regimens, the GDG proposes that programmes that implement this regimen should aim for more frequent culture testing, especially after the intensive phase, to confirm bacteriological cure in patients who complete treatment without signs of failure. Any sign of recurrence after termination of treatment should also be investigated using sputum smear microscopy, culture and DST.

5.4 Implementation considerations

Good-quality sputum specimens are necessary to ensure that laboratories can diagnose TB properly. In addition, laboratories should have sufficient space to ensure the quality, safety and efficiency of the services provided to clients whose samples are tested, and to ensure the safety of laboratory personnel, patients and visitors *(107)*. Some countries experience difficulties with the implementation and quality assurance of sputum culture, which affects this recommendation because it is dependent on access to quality-assured laboratories that can offer TB culture. Sputum smear and culture examinations are also dependent on the quality of the sputum produced, so care should be taken to obtain adequate specimens and transport them to the laboratory according to standard procedures, to maintain the viability of the bacilli and thus obtain a valid culture result.

In programmatic settings, the practitioner treating MDR-TB patients is typically guided not only by bacteriological tests but also by markers of response to treatment or of disease progression, such as the patient's general condition, weight gain over time, resolution of disease manifestations, blood

indices and results of imaging (e.g. chest radiography). The potential use of Xpert MTB/RIF assay in monitoring treatment response has yet to be determined *(108, 109)*.

The implementation of more frequent microbiological testing would require appropriate resources to be made available, both for the laboratories undertaking the tests and for the patient, who may have to spend more time visiting the facilities and, at times, pay for the testing. Patient values and preferences need to be considered to ensure a more acceptable service and patient-centred delivery of care. Increased monitoring should not be done at the expense of overburdening the laboratory services or upsetting health equity by displacing resources from other essential components of the programme.

5.5 Monitoring and evaluation

Culture and microscopy results for tests performed in patients on MDR-TB treatment should be captured in the second-line TB treatment register as well as the respective laboratory registers *(79)*. Sometimes these registers may exist as part of an electronic laboratory or patient information system, which makes it much easier for multiple users to access the data in real time and can also help to limit errors. It is important for the programme manager to assess the records in the second-line TB treatment register for completeness of testing using both culture and sputum smear microscopy, any discordance between the two modalities, and whether decisions on regimen changes or assignment of outcome are coherent (e.g. does a case have sufficient negative culture test results available to be classified as "cured"?). Performance indicators help to improve the quality of care; such indicators include contamination rates, turnaround times and proportion of culture tests done without results being recorded in the patient information system. In the case of repeated positive cultures, repeat testing for drug susceptibility or resistance is important.

Section 6. Starting antiretroviral therapy in patients on MDR/RR-TB regimens

6.1 Recommendation

No.	Recommendation
6.1	Antiretroviral therapy is recommended for all patients with HIV and drug-resistant tuberculosis requiring second-line antituberculosis drugs, irrespective of CD4 cell count, as early as possible (within the first 8 weeks) following initiation of antituberculosis treatment. *(Strong recommendation, very low certainty of evidence)*

6.2 Justification and evidence

The recommendation in this section addresses one PICO question:

PICO question *(DR-TB, 2011): In patients with HIV infection and drug-resistant TB receiving antiretroviral therapy, is the use of drugs with overlapping and potentially additive toxicities, compared with their avoidance, more or less likely to lead to cure or other outcomes?*[48]

Evidence was reviewed from 10 studies *(110–119)*, to assess patient treatment outcomes when ART and second-line antituberculosis drugs were used together. None of the data were from RCTs. IPD were available for 217 patients with DR-TB, of whom 127 received ART. The level of evidence in individual observational studies varied from low to very low quality.

6.3 Summary of findings

The pooled IPD from longitudinal cohort studies showed a lower risk of death and a higher likelihood of cure, and resolution of TB signs and symptoms in patients using ART, compared with those not using ART (low-quality evidence). There is very low certainty evidence for other outcomes that were considered critical or important for decision-making (e.g. severe adverse effects from second-line drugs for DR-TB, occurrence of sputum smear or culture conversion, interactions of ART with antituberculosis drugs and default from treatment). Available data did not allow assessment for several other outcomes of interest; namely, avoiding the acquisition of additional drug resistance, preventing TB transmission, sustaining relapse-free cure, establishing the optimal duration of MDR-TB treatment, avoiding unnecessary MDR-TB treatment, reducing costs and improving population access to appropriate care.

6.4 Benefits

The strong recommendation for the use of ART is based in part on indirect evidence from its use in any patient with active TB, which shows large beneficial effects and a very high mortality when ART is not employed *(120)* particularly in highly immunocompromised patients (CD4 cell count <50 cells/mm3) *(121, 122)*. In the absence of other data specific to patients with DR-TB receiving second-line antituberculosis medication, the decision on when to start ART should be no different from the approach to a patient living with HIV with drug-susceptible TB. ART should thus be initiated regardless of CD4 cell count and as soon as antituberculosis treatment is tolerated, ideally as early as 2 weeks and no later than 8 weeks after initiation of antituberculosis treatment *(120, 123)*. However, for TB patients living with HIV with profound immunosuppression (e.g. CD4 counts <50 cells/mm^3), they should receive ART within the first 2 weeks of initiating TB treatment *(96)*.

6.5 Risks

The successful implementation of this recommendation will depend on the availability of more providers trained specifically in the care of HIV and DR-TB, and drug–drug interactions. A substantial increase in the availability of and patient's access to treatment, and additional support for ensuring adherence would probably be needed. The need for increased integration of HIV and TB care for effective patient management, prompt evaluation of adverse events and case-holding throughout treatment will necessitate more resources. Updated information on drug–drug interactions between antiretroviral and antituberculosis medicines is now available online *(36)*.

[48] The outcomes considered for this question comprised: 1. Cure (treatment failure), 2. Prompt initiation of appropriate treatment, 3. Avoiding the acquisition or amplification of drug resistance, 4. Survival (death from TB), 5. Staying disease-free after treatment; sustaining a cure (relapse), 6. Case-holding so the TB patient remains adherent to treatment (default or treatment interruption due to non-adherence), 7. Population coverage or access to appropriate treatment of DR-TB, 8. Smear or culture conversion during treatment, 9. Accelerated detection of drug resistance, 10. Avoidance of unnecessary MDR-TB treatment, 11. Population coverage or access to diagnosis of DR-TB, 12. Prevention or interruption of transmission of DR-TB to other people, including other patients and health care workers, 13. Shortest possible duration of treatment, 14. Avoiding toxicity and adverse reactions from antituberculosis drugs, 15. Cost to the patient, including direct medical costs and other costs such as transportation and lost wages due to disability, 16. Resolution of TB signs and symptoms; ability to resume usual life activities, 17. Interaction of antituberculosis drugs with non-TB medications, and 18. Cost to the TB control programme.

6.6 Values and preferences

A high value was placed on outcomes such as prevention of early death and TB transmission, and a lower value was placed on the resources required to make ART available to all MDR-TB patients infected with HIV.

Section 7. Surgery for patients on MDR/RR-TB treatment

7.1 Recommendation

No.	Recommendation
7.1	In patients with rifampicin-resistant tuberculosis (RR-TB) or multidrug-resistant TB (MDR-TB), elective partial lung resection (lobectomy or wedge resection) may be used alongside a recommended MDR-TB regimen. *(Conditional recommendation, very low certainty of evidence)*

7.2 Justification and evidence

The recommendation in this section addresses one PICO question:

PICO question *(DR-TB, 2016): Among patients on MDR-TB treatment, are the following two interventions (delay in start of treatment and elective surgery) likely to lead to cure and other outcomes?*[49]

Surgery has been employed in treating TB patients since before the advent of chemotherapy. In many countries, it remains one of the treatment options for TB. With the challenging prospect in many settings of inadequate regimens to treat DR-TB, and the risk of serious sequelae, the role of pulmonary surgery is being re-evaluated as a way to reduce the amount of lung tissue with intractable pathology and reduce bacterial load, and thus improve prognosis. The review for this question was based on both an IPD meta-analysis to evaluate the effectiveness of different forms of elective surgery as an adjunct to combination medical therapy for MDR-TB *(124)*, and a systematic review and study-level meta-analysis *(125)*. Demographic, clinical, bacteriological, surgical and outcome data of MDR-TB patients on treatment were obtained from the authors of 26 cohort studies that supplied data for the adult IPD (aIPD) *(55)*. The analyses summarized in the GRADE tables consist of three strata comparing treatment success (e.g. cure and completion) with different combinations of treatment failure, relapse, death and loss to follow-up. Two sets of such tables were prepared, one for partial pulmonary resection and one for pneumonectomy. Based on an assessment of the certainty of the evidence, carried out using predefined criteria and documented in GRADEpro, the certainty of the evidence was rated as very low to low, depending on the outcome being assessed and type of study.

In the study-level meta-analysis that examined all forms of surgery together, there was a statistically significant improvement in cure and successful treatment outcomes among patients who received surgery. However, when the aIPD meta-analysis examined patients who underwent partial lung resection and those who had a more radical pneumonectomy compared with patients who did not undergo surgery, those who underwent partial lung resection had statistically significantly higher rates of treatment success. Patients who underwent pneumonectomy did not have better outcomes than those who did not undergo surgery. Prognosis appeared to be better when partial lung resection

[49] The outcomes comprise 1. Cured/completed by end of treatment, 2. Culture conversion by 6 months, 3. Failure, 4. Relapse, 5. Survival (or death), 6. Adverse reactions (severity, type, organ class), and 7. Adherence to treatment (or treatment interruption due to non-adherence).

was performed after culture conversion. This effect was not observed in patients who underwent pneumonectomy. There are several important caveats to these data. Substantial bias is likely to be present, because only patients judged to be fit for surgery would have been operated on. No patient with HIV coinfection in the aIPD underwent lung resection surgery. Therefore, the effects of surgery among PLHIV with MDR-TB could not be evaluated. Rates of death did not differ significantly between those who underwent surgery and those who received medical treatment only. However, the outcomes could be biased because the risk of death could have been much higher among patients in whom surgery was prescribed had they not been operated on.

7.3 Subgroup considerations

The relative benefits of surgery are expected to depend substantially on the population subgroups that are targeted. The analysis could not provide a refined differentiation of the type of patient who would be best suited to benefit from the intervention or the type of intervention that would have the most benefit. The effect is expected to be moderate in the average patient considered appropriate for surgery. The odds of success for patients with XDR-TB (pre-2021 definition) were statistically significantly lower when they underwent surgery compared with other patients (aOR: 0.4, 95% CL: 0.2–0.9). This effect is likely to be biased, given that patients who underwent surgery would have had other factors predisposing to poor outcomes that could not be adjusted for.

7.4 Implementation considerations

Partial lung resection for patients with MDR-TB is to be considered only under conditions of good surgical facilities and trained and experienced surgeons, and with careful selection of candidates.

7.5 Monitoring and evaluation

The rates of death in the IPD for surgical outcomes did not differ significantly between patients who underwent surgery and those who received medical treatment only. There were not enough data on adverse events, surgical complications or long-term sequelae – some of which may be fatal – to allow a meaningful analysis. Despite the unknown magnitude of perioperative complications, the GDG assumed that, overall, there is a net benefit from surgery.

Research gaps

In addition to summarizing the available evidence, the reviews undertaken for these consolidated guidelines revealed several gaps in current knowledge about critical areas in DR-TB treatment and care. The estimates of effect for patient studies were commonly assigned a low or very low certainty rating, which explains why most of the recommendations in these guidelines are conditional. Some gaps persist from those identified in previous TB treatment guidelines *(11, 12)*. When completing the GRADE evidence-to-decision tables, there was a lack of studies on how patients, caregivers and other stakeholders value different treatment options and outcomes (e.g. time to sputum conversion, cure, treatment failure and relapse, death and serious adverse events). Areas that would be relevant to many priority questions in the programmatic management of DR-TB include implementation research; studies of resource use; incremental cost, acceptability, feasibility and equity; values and preferences of patients and health care workers; and the inclusion of indicators of quality of life.

The research gaps that were identified by the successive GDGs are grouped by the respective sections of these guidelines, although some are interlinked.

Section 1. The 6-month BPaLM regimen for treatment of MDR/RR-TB or pre-XDR-TB

Further research is needed in the following areas:

a. the efficacy, safety and tolerability of the BPaLM/BPaL regimen for subpopulations for whom current data are limited or missing; that is, children aged below 14 years, patients with extrapulmonary TB, PLHIV with CD4 counts below 100, and pregnant and lactating women;

b. data from other regions and countries (beyond countries with sites included in recent studies);

c. description of the mechanism and molecular markers of pretomanid resistance, allowing development of the DST, clinical implications of the lineage 1 effect on efficacy of pretomanid,[50] cross-resistance with delamanid and surveillance for the development of resistance, with adequate consideration paid to the impact of selected mutations;

d. documenting the full adverse event profile of pretomanid, and the frequency of relevant adverse events, with a focus on hepatotoxicity and reproductive toxicity in humans (studies ongoing);

e. exploring the relative efficacy (and added value in multidrug regimens) of pretomanid and delamanid;

f. studies capturing outcomes for which currently evidence is scarce (e.g. acquisition of drug resistance and quality of life);

g. research on geographical differences in the frequency and severity of linezolid-related adverse events and the underlying cause (north–south differences were observed in post-hoc analyses of large and unexplained differences in linezolid-related adverse events between sites);

h. exploring the possibility of replacing moxifloxacin with levofloxacin;

i. exploring the extent of cross-resistance between bedaquiline and clofazimine;

[50] A lineage effect is observed for lineage 1 strains that are shown to exhibit higher MICs than other lineages in vitro. The in vivo clinical significance of such an effect is unknown (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9155602/).

j. monitoring of resistance to new and repurposed medicines;

k. exploring methods to ensure treatment adherence;

l. exploring regimen composition when the new generation of component medicines are available; and

m. exploring the efficacy of other 6-month regimens.

Section 2. The 9-month all-oral regimen for MDR/RR-TB

Further research is needed in the following areas:

a. the effectiveness and safety of variants of the shorter MDR-TB treatment regimen, in which the injectable agent is replaced by an oral agent (e.g. bedaquiline) and the total duration is reduced to 6 months or less;

b. comparison of the effectiveness of these variants of the shorter regimen in:

   i. patient subgroups that have often been systematically excluded from studies or country programme cohorts (e.g. children, patients with additional resistance, those with extrapulmonary TB, and pregnant or breastfeeding women);

   ii. settings where background resistance to drugs other than fluoroquinolones and second-line injectable agents is high (e.g. pyrazinamide or high-level isoniazid resistance);

c. additional RCTs and ORs on all-oral shorter MDR-TB treatment regimens, also allowing comparison of all-oral shorter regimens to all-oral longer regimens;

d. programmatic data from countries other than South Africa;

e. data from children, pregnant women, older people, patients with diabetes and other special populations;

f. data on patients presenting with extensive TB disease;

g. information on the frequency and mechanisms of bedaquiline resistance acquisition, and the genetic markers that indicate probable resistance; and

h. identification of optimal companion drugs that protect bedaquiline and limit the acquisition of bedaquiline resistance, including consideration of the need to protect the long "tail" of potential single drug exposure (given its exceptionally long half-life) if bedaquiline is stopped at the same time as companion drugs.

Section 3. Longer regimens for MDR/RR-TB

Further research is needed in the following areas:

a. the optimal combination of medicines and the approach to regimen design for adults and children with MDR/RR-TB, with or without additional resistance to key agents;

b. RCTs, which are lacking, especially those involving new drugs and regimens – the release of results from the first Phase 3 trials for MDR-TB has led to debate about the clinical relevance of the design and endpoints chosen for these studies, requiring at times additional, off-protocol analysis of data to explore the potential added value of the experimental interventions;

c. inclusion and separate reporting of outcomes for key subgroups in RCTs, especially children, pregnant and breastfeeding women, and PLHIV on treatment;

d. studies of pharmacokinetics and safety to determine optimal drug dosing (especially in pregnancy), and the effect of extemporaneous manipulation of existing dosing forms;

e. complete recording of adverse events and standardized data on organ class, seriousness, severity and certainty of association to allow meaningful comparison of the association between

adverse events and exposure to different medicines between studies, patient subgroups and different regimens;

f. determination of the minimum number of drugs and treatment duration (especially in patients previously treated for MDR-TB);

g. improved diagnostics and DST methods (e.g. which test to use for resistance to pyrazinamide) especially for medicines for which no rapid molecular methods are currently available in the field;

h. further research and development would be particularly helpful for the following agents:

   i. *levofloxacin:* optimization of the dose – the Opti-Q study will soon provide new information on this *(126)*;

   ii. *bedaquiline:* optimization of the duration in both adults and children, and use during pregnancy;

   iii. *linezolid:* optimization of the dose and duration in both adults and children, and patient predictors for adverse reactions;

   iv. *clofazimine:* optimization of the dose especially in children, any added value in using a loading dose and availability of DST methods;

   v. *cycloserine and terizidone:* differences in efficacy between the two medicines, approaches to test for susceptibility to them, and best practices in psychiatric care for people on these medicines;

   vi. *delamanid:* better understanding of its role in MDR-TB regimens, including in children (pharmacokinetics and pharmacodynamics), PLHIV and pregnant women; mechanisms of development of drug resistance; and optimization of the duration in both adults and children;

   vii. *pyrazinamide:* molecular testing for resistance (pursuing either LPA or other approaches);

   viii. *carbapenems:* given their effectiveness in the evidence reviews, further research on their role in MDR-TB regimens is important, including the potential role and cost–effectiveness of ertapenem (which can be given intramuscularly) as a substitute for meropenem and imipenem–cilastatin;

   ix. *amikacin:* the safety and effectiveness of thrice-weekly administration at a higher dose (about 25 mg/kg per day) *(78)*;

j. identification of factors that determine the optimal duration of treatment (e.g. previous treatment history, baseline resistance patterns, site of disease and age); and

k. exploration of strategies to optimize the balance of benefits versus harms of regimen duration through risk-stratification approaches.

Section 4. Regimens for rifampicin-susceptible, isoniazid-resistant TB (Hr-TB)

The development of the current recommendations was made possible by the availability of a global Hr-TB IPD. As in other IPD analyses conducted to inform WHO treatment guidelines in recent years, the Hr-TB IPD analysis facilitated the comparison of different patient groups, some adjustment for covariates and better interpretation of the results *(57)*. It is important for researchers and national programmes to continue contributing patient records to the Hr-TB IPD, to increase its value as a source of information for future treatment policy.

All the recommendations were conditional and were based on very low certainty in the estimates of effect; thus, further research is needed to inform the refinement of policies to optimize the treatment of Hr-TB. The GDG identified various research priorities, including the following:

a. the need for RCTs evaluating the efficacy, safety and tolerability of regimens for Hr-TB, and for cases with additional resistance to other medicines such as ethambutol or pyrazinamide (e.g. polydrug resistance);

b. research to clarify the potential benefits and risks of treatment with high-dose isoniazid;
c. high-quality studies on optimizing the composition and duration of regimens in children and adults, particularly of high-dose isoniazid, fluoroquinolones and other second-line medicines, and of reducing the duration of pyrazinamide;
d. modelling studies to estimate the number-needed-to-treat for empirical use of an Hr-TB regimen, balancing risks and benefits;
e. high-quality studies on treatment prolongation among PLHIV;
f. high-quality studies evaluating regimens for extrapulmonary or disseminated TB;
g. feasibility of developing FDCs for REZ alone (with or without integrating levofloxacin);
h. monitoring patient response by isoniazid resistance genotype (e.g. *kat*G versus *inh*A mutations), either in an individual patient or in a population;
i. cost–effectiveness of different approaches to DST, including rapid testing of all TB patients for both isoniazid and rifampicin resistance before the start of treatment;
j. participatory action research within communities and with other stakeholders (e.g. field practitioners and community workers) to explore sociocultural factors that can facilitate treatment adherence and influence outcomes; and
k. effect of underlying fluoroquinolones and isoniazid polydrug resistance on treatment outcomes.

Section 5. Monitoring patient response to MDR/RR-TB treatment using culture

Further research is needed in the following areas:

a. analysis of the predictors and biomarkers of treatment failure (related to strain, regimen and host), and of the bacteriological response, in the following important subgroups, which would help to identify more resource-saving options and reduce the time needed to make decisions:
    i. patients aged below 15 years;
    ii. patients with extrapulmonary disease (different forms);
    iii. patients on shorter MDR-TB regimens (standardized or all-oral variants);
b. continuing to assess the potential role of future-generation rapid molecular testing beyond diagnostic testing to also monitor the treatment response; and
c. evaluation of the engineering challenges to implementing more affordable liquid culture systems.

Section 6. Starting antiretroviral therapy in patients on MDR/RR-TB regimens

No research gaps were identified.

Section 7. Surgery for patients on MDR/RR-TB treatment

Further research is needed in the following areas:

a. the role of surgery – that is, decisions about when to operate, and the type of surgical intervention, and drug-resistance patterns; and
b. improved collection, reporting and standardization of data on surgery, including long-term survival post-surgery.

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Annex 1. Supplementary table

Summary of changes to the World Health Organization (WHO) treatment recommendations for multidrug-resistant or rifampicin-resistant TB (MDR/RR-TB) between 2019, 2020 and the current update (in 2022).

Notes:

- The *WHO consolidated guidelines on drug-resistant tuberculosis treatment* are a collection of currently valid and new recommendations on the treatment and management of MDR/RR-TB; as such, they include new recommendations developed in 2022 and all valid recommendations that had been previously published.
- In the current update (2022), there are two new recommendations (Recommendations 1.1 and 2.1). Recommendation 1.1 is a development based on new evidence on the bedaquiline, pretomanid, linezolid and moxifloxacin (BPaLM)/bedaquiline, pretomanid and linezolid (BPaL) regimen and Recommendation 2.1 is an update to a previous recommendation on shorter regimens for MDR/RR-TB.
- Recommendations on the use of bedaquiline and delamanid in children aged below 3 and 6 years were added from the *WHO consolidated guidelines on tuberculosis. Module 5. Management of tuberculosis in children and adolescents*.
- Recommendations on TB care and support are grouped in a separate submodule of the *WHO consolidated guidelines on tuberculosis. Module 4. Treatment*.
- All other recommendations remain unchanged.

Recommendations in the 2019 update	Recommendations in the 2020 update	Recommendations in the 2022 update
Not included in the 2019 guidelines	**Section 4: The bedaquiline, pretomanid and linezolid (BPaL) regimen for MDR-TB with additional fluoroquinolone resistance**	**Section 1: The 6-month bedaquiline, pretomanid, linezolid and moxifloxacin (BPaLM) regimen for MDR/RR-TB or pre-XDR-TB**
Not included the in 2019 guidelines	**4.1** A treatment regimen lasting 6–9 months, composed of bedaquiline, pretomanid and linezolid (BPaL), may be used under operational research conditions in multidrug-resistant tuberculosis (MDR-TB) patients with TB that is resistant to fluoroquinolones, who have either had no previous exposure to bedaquiline and linezolid or have been exposed for no more than 2 weeks. *(Conditional recommendation, very low certainty in the estimates of effect)* ***(New recommendation)***	**1.1** WHO suggests the use of the 6-month treatment regimen, composed of bedaquiline, pretomanid, linezolid (600 mg) and moxifloxacin (BPaLM), rather than 9-month or longer (18-month) regimens in MDR/RR-TB patients. *(Conditional recommendation, very low certainty of evidence)* ***(New recommendation, replacing 4.1 in the 2020 update)***
Section 4: Use of the standardized shorter MDR-TB regimen	**Section 2: Shorter, all-oral, bedaquiline-containing regimen for multidrug-/rifampicin-resistant tuberculosis**	**Section 2: The 9-month all-oral regimen for MDR/RR-TB**
In MDR/RR-TB patients who have not been previously treated for more than 1 month with second-line medicines used in the shorter MDR-TB regimen or in whom resistance to fluoroquinolones and second-line injectable agents has been excluded, a shorter MDR-TB regimen of 9–12 months may be used instead of the longer regimens. *(Conditional recommendation, low certainty in the estimates of effect)*	2.1 A shorter all-oral bedaquiline-containing regimen of 9–12 months duration is recommended in eligible patients with confirmed multidrug- or rifampicin-resistant tuberculosis (MDR/RR-TB) who have not been exposed to treatment with second-line TB medicines used in this regimen for more than 1 month, and in whom resistance to fluoroquinolones has been excluded. *(Conditional recommendation, very low certainty in the evidence)* *(Updated recommendation)*	**2.1** WHO suggests the use of the 9-month all-oral regimen rather than longer (18-month) regimens in patients with MDR/RR-TB and in whom resistance to fluoroquinolones has been excluded *(Conditional recommendation, very low certainty of evidence)* ***(New recommendation, replacing 2.1 in the 2020 update)***

Recommendations in the 2019 update	Recommendations in the 2020 update	Recommendations in the 2022 update
Section 2: The composition of longer MDR-TB regimens	**Section 3: Longer regimens for multidrug-/ rifampicin-resistant tuberculosis**	**Section 3: Longer regimens for MDR/RR-TB**
In MDR/RR-TB patients on longer regimens, all three Group A agents and at least one Group B agent should be included to ensure that treatment starts with at least four TB agents likely to be effective, and that at least three agents are included for the rest of the treatment after bedaquiline is stopped.[51] If only one or two Group A agents are used, both Group B agents are to be included. If the regimen cannot be composed with agents from Groups A and B alone, Group C agents are added to complete it. *(Conditional recommendation, very low certainty in the estimates of effect)*	3.1 In multidrug- or rifampicin-resistant tuberculosis (MDR/RR-TB) patients on longer regimens, all three Group A agents and at least one Group B agent should be included to ensure that treatment starts with at least four TB agents likely to be effective, and that at least three agents are included for the rest of treatment if bedaquiline is stopped. If only one or two Group A agents are used, both Group B agents are to be included. If the regimen cannot be composed with agents from Groups A and B alone, Group C agents are added to complete it. *(Conditional recommendation, very low certainty in the estimates of effect)* *(Editing of the word "after" to "if" with reference to stopping bedaquiline)*	3.1 In multidrug- or rifampicin-resistant tuberculosis (MDR/RR-TB) patients on longer regimens, all three Group A agents and at least one Group B agent should be included to ensure that treatment starts with at least four TB agents likely to be effective, and that at least three agents are included for the rest of the treatment if bedaquiline is stopped. If only one or two Group A agents are used, both Group B agents are to be included. If the regimen cannot be composed with agents from Groups A and B alone, Group C agents are added to complete it. *(Conditional recommendation, very low certainty of evidence)* *(No change)*
Kanamycin and capreomycin are not to be included in the treatment of MDR/RR-TB patients on longer regimens. *(Conditional recommendation, very low certainty in the estimates of effect)*	3.2 Kanamycin and capreomycin are not to be included in the treatment of MDR/RR-TB patients on longer regimens. *(Conditional recommendation, very low certainty in the estimates of effect)* *(No change)*	3.2 Kanamycin and capreomycin are not to be included in the treatment of MDR/RR-TB patients on longer regimens. *(Conditional recommendation, very low certainty of evidence)* *(No change)*

[51] Group A = levofloxacin/moxifloxacin, bedaquiline, linezolid; Group B = clofazimine, cycloserine/terizidone; Group C = ethambutol, delamanid, pyrazinamide, imipenem–cilastatin, meropenem, amikacin (streptomycin), ethionamide/prothionamide, p-aminosalicylic acid (see also Table 3.1).

Recommendations in the 2019 update	Recommendations in the 2020 update	Recommendations in the 2022 update
Levofloxacin or moxifloxacin should be included in the treatment of MDR/RR-TB patients on longer regimens. *(Strong recommendation, moderate certainty in the estimates of effect)*	3.3 Levofloxacin or moxifloxacin should be included in the treatment of MDR/RR-TB patients on longer regimens. *(Strong recommendation, moderate certainty in the estimates of effect)* *(No change)*	3.3 Levofloxacin or moxifloxacin should be included in the treatment of MDR/RR-TB patients on longer regimens. *(Strong recommendation, moderate certainty of evidence)* *(No change)*
Bedaquiline should be included in longer MDR-TB regimens for patients aged 18 years or more. *(Strong recommendation, moderate certainty in the estimates of effect)* Bedaquiline may also be included in longer MDR-TB regimens for patients aged 6–17 years. *(Conditional recommendation, very low certainty in the estimates of effect)*	3.4 Bedaquiline should be included in longer multidrug-resistant TB (MDR-TB) regimens for patients aged 18 years or more. *(Strong recommendation, moderate certainty in the estimates of effect)* Bedaquiline may also be included in longer MDR-TB regimens for patients aged 6–17 years. *(Conditional recommendation, very low certainty in the estimates of effect)* *(No change)*	3.4 Bedaquiline should be included in longer multidrug-resistant TB (MDR-TB) regimens for patients aged 18 years or more. *(Strong recommendation, moderate certainty of evidence)* *(No change)* Bedaquiline may also be included in longer MDR-TB regimens for patients aged 6–17 years. *(Conditional recommendation, very low certainty of evidence)* *(No change)* In children with MDR/RR-TB aged below 6 years, an all-oral treatment regimen containing bedaquiline may be used. *(Conditional recommendation, very low certainty of evidence)* *(New and additional recommendation)*
Linezolid should be included in the treatment of MDR/RR-TB patients on longer regimens. *(Strong recommendation, moderate certainty in the estimates of effect)*	3.5 Linezolid should be included in the treatment of MDR/RR-TB patients on longer regimens. *(Strong recommendation, moderate certainty in the estimates of effect)* *(No change)*	3.5 Linezolid should be included in the treatment of MDR/RR-TB patients on longer regimens. *(Strong recommendation, moderate certainty of evidence)* *(No change)*

Recommendations in the 2019 update	Recommendations in the 2020 update	Recommendations in the 2022 update
Clofazimine and cycloserine or terizidone may be included in the treatment of MDR/RR-TB patients on longer regimens. *(Conditional recommendation, very low certainty in the estimates of effect)*	3.6 Clofazimine and cycloserine or terizidone may be included in the treatment of MDR/RR-TB patients on longer regimens. *(Conditional recommendation, very low certainty in the estimates of effect)* *(No change)*	3.6 Clofazimine and cycloserine or terizidone may be included in the treatment of MDR/RR-TB patients on longer regimens. *(Conditional recommendation, very low certainty of evidence)* *(No change)*
Ethambutol may be included in the treatment of MDR/RR-TB patients on longer regimens. *(Conditional recommendation, very low certainty in the estimates of effect)*	3.7 Ethambutol may be included in the treatment of MDR/RR-TB patients on longer regimens. *(Conditional recommendation, very low certainty in the estimates of effect)* *(No change)*	3.7 Ethambutol may be included in the treatment of MDR/RR-TB patients on longer regimens. *(Conditional recommendation, very low certainty of evidence)* *(No change)*
Delamanid may be included in the treatment of MDR/RR-TB patients aged 3 years or more on longer regimens. *(Conditional recommendation, moderate certainty in the estimates of effect)*	3.8 Delamanid may be included in the treatment of MDR/RR-TB patients aged 3 years or more on longer regimens. *(Conditional recommendation, moderate certainty in the estimates of effect)* *(No change)*	3.8 Delamanid may be included in the treatment of MDR/RR-TB patients aged 3 years or more on longer regimens. *(Conditional recommendation, moderate certainty of evidence)* *(No change)* In children with MDR/RR-TB aged below 3 years delamanid may be used as part of longer regimens. *(Conditional recommendation, very low certainty of evidence)* *(New and additional recommendation)*
Pyrazinamide may be included in the treatment of MDR/RR-TB patients on longer regimens. *(Conditional recommendation, very low certainty in the estimates of effect)*	3.9 Pyrazinamide may be included in the treatment of MDR/RR-TB patients on longer regimens. *(Conditional recommendation, very low certainty in the estimates of effect)* *(No change)*	3.9 Pyrazinamide may be included in the treatment of MDR/RR-TB patients on longer regimens. *(Conditional recommendation, very low certainty of evidence)* *(No change)*

Recommendations in the 2019 update	Recommendations in the 2020 update	Recommendations in the 2022 update
Imipenem–cilastatin or meropenem may be included in the treatment of MDR/RR-TB patients on longer regimens. *(Conditional recommendation, very low certainty in the estimates of effect)*	3.10 Imipenem–cilastatin or meropenem may be included in the treatment of MDR/RR-TB patients on longer regimens. *(Conditional recommendation, very low certainty in the estimates of effect)*[52] *(No change)*	3.10 Imipenem–cilastatin or meropenem may be included in the treatment of MDR/RR-TB patients on longer regimens. *(Conditional recommendation, very low certainty of evidence)*[1] *(No change)*
Amikacin may be included in the treatment of MDR/RR-TB patients aged 18 years or more on longer regimens when susceptibility has been demonstrated and adequate measures to monitor for adverse reactions can be ensured. If amikacin is not available, streptomycin may replace amikacin under the same conditions. *(Conditional recommendation, very low certainty in the estimates of effect)*	3.11 Amikacin may be included in the treatment of MDR/RR-TB patients aged 18 years or more on longer regimens when susceptibility has been demonstrated and adequate measures to monitor for adverse reactions can be ensured. If amikacin is not available, streptomycin may replace amikacin under the same conditions. *(Conditional recommendation, very low certainty in the estimates of effect)* *(No change)*	3.11 Amikacin may be included in the treatment of MDR/RR-TB patients aged 18 years or more on longer regimens when susceptibility has been demonstrated and adequate measures to monitor for adverse reactions can be ensured. If amikacin is not available, streptomycin may replace amikacin under the same conditions. *(Conditional recommendation, very low certainty of evidence)* *(No change)*
Ethionamide or prothionamide may be included in the treatment of MDR/RR-TB patients on longer regimens only if bedaquiline, linezolid, clofazimine or delamanid are not used, or if better options to compose a regimen are not possible. *(Conditional recommendation against use, very low certainty in the estimates of effect)*	3.12 Ethionamide or prothionamide may be included in the treatment of MDR/RR-TB patients on longer regimens only if bedaquiline, linezolid, clofazimine or delamanid are not used, or if better options to compose a regimen are not possible. *(Conditional recommendation against use, very low certainty in the estimates of effect)* *(No change)*	3.12 Ethionamide or prothionamide may be included in the treatment of MDR/RR-TB patients on longer regimens only if bedaquiline, linezolid, clofazimine or delamanid are not used, or if better options to compose a regimen are not possible. *(Conditional recommendation against use, very low certainty of evidence)* *(No change)*

[52] Imipenem–cilastatin and meropenem are administered with clavulanic acid, which is available only in formulations combined with amoxicillin. Amoxicillin–clavulanic acid is not counted as an additional effective TB agent, and should not be used without imipenem– cilastatin or meropenem.

Recommendations in the 2019 update	Recommendations in the 2020 update	Recommendations in the 2022 update
P-aminosalicylic acid may be included in the treatment of MDR/RR-TB patients on longer regimens only if bedaquiline, linezolid, clofazimine or delamanid are not used or if better options to compose a regimen are not possible. *(Conditional recommendation against use, very low certainty in the estimates of effect)*	3.13 *P*-aminosalicylic acid may be included in the treatment of MDR/RR-TB patients on longer regimens only if bedaquiline, linezolid, clofazimine or delamanid are not used, or if better options to compose a regimen are not possible. *(Conditional recommendation against use, very low certainty in the estimates of effect)* *(No change)*	3.13 *P*-aminosalicylic acid may be included in the treatment of MDR/RR-TB patients on longer regimens only if bedaquiline, linezolid, clofazimine or delamanid are not used, or if better options to compose a regimen are not possible. *(Conditional recommendation against use, very low certainty of evidence)* *(No change)*
Clavulanic acid should not be included in the treatment of MDR/RR-TB patients on longer regimens. *(Strong recommendation against use, low certainty in the estimates of effect)*[53]	3.14 Clavulanic acid should not be included in the treatment of MDR/RR-TB patients on longer regimens. *(Strong recommendation against use, low certainty in the estimates of effect)*[1] *(No change)*	3.14 Clavulanic acid should not be included in the treatment of MDR/RR-TB patients on longer regimens. *(Strong recommendation against use, low certainty of evidence)*[1] *(No change)*
Section 3: The duration of longer MDR-TB regimens	**Section 3: Longer regimens for multidrug-/ rifampicin-resistant tuberculosis**	**Section 3: Longer regimens for MDR/RR-TB**
In MDR/RR-TB patients on longer regimens, a total treatment duration of 18–20 months is suggested for most patients; the duration may be modified according to the patient's response to therapy. *(Conditional recommendation, very low certainty in the estimates of effect)*	3.15 In MDR/RR-TB patients on longer regimens, a total treatment duration of 18–20 months is suggested for most patients; the duration may be modified according to the patient's response to therapy. *(Conditional recommendation, very low certainty in the estimates of effect)* *(No change to wording but combined with section above called: Section 3: Recommendations on the use of longer regimens for multidrug-/ rifampicin-resistant tuberculosis)*	3.15 In MDR/RR-TB patients on longer regimens, a total treatment duration of 18–20 months is suggested for most patients; the duration may be modified according to the patient's response to therapy. *(Conditional recommendation, very low certainty of evidence)* *(No change)*

[53] Imipenem–cilastatin and meropenem are administered with clavulanic acid, which is available only in formulations combined with amoxicillin (amoxicillin–clavulanic acid). When included, clavulanic acid is not counted as an additional effective TB agent and should not be used without imipenem–cilastatin or meropenem.

Recommendations in the 2019 update	Recommendations in the 2020 update	Recommendations in the 2022 update
In MDR/RR-TB patients on longer regimens, a treatment duration of 15–17 months after culture conversion is suggested for most patients; the duration may be modified according to the patient's response to therapy. *(Conditional recommendation, very low certainty in the estimates of effect)*	3.16 In MDR/RR-TB patients on longer regimens, a treatment duration of 15–17 months after culture conversion is suggested for most patients; the duration may be modified according to the patient's response to therapy. *(Conditional recommendation, very low certainty in the estimates of effect)* *(No change to wording but combined with section above called: Section 3: Recommendations on the use of longer regimens for multidrug-/ rifampicin-resistant tuberculosis)*	3.16 In MDR/RR-TB patients on longer regimens, a treatment duration of 15–17 months after culture conversion is suggested for most patients; the duration may be modified according to the patient's response to therapy. *(Conditional recommendation, very low certainty of evidence)* *(No change)*
In MDR/RR-TB patients on longer regimens that contain amikacin or streptomycin, an intensive phase of 6–7 months is suggested for most patients; the duration may be modified according to the patient's response to therapy. *(Conditional recommendation, very low certainty in the estimates of effect)*	3.17 In MDR/RR-TB patients on longer regimens containing amikacin or streptomycin, an intensive phase of 6–7 months is suggested for most patients; the duration may be modified according to the patient's response to therapy. *(Conditional recommendation, very low certainty in the estimates of effect)* *(No substantive change to wording but combined with section above called: Section 2.2: Recommendations on the use of longer regimens for multidrug-/ rifampicin-resistant tuberculosis)*	3.17 In MDR/RR-TB patients on longer regimens containing amikacin or streptomycin, an intensive phase of 6–7 months is suggested for most patients; the duration may be modified according to the patient's response to therapy. *(Conditional recommendation, very low certainty of evidence)* *(No change)*

Recommendations in the 2019 update	Recommendations in the 2020 update	Recommendations in the 2022 update
Section 1: Regimens for isoniazid-resistant tuberculosis	**Section 1: Regimen for rifampicin-susceptible and isoniazid-resistant tuberculosis**	**Section 4: Regimen for rifampicin-susceptible and isoniazid-resistant tuberculosis**
In patients with confirmed rifampicin-susceptible and isoniazid-resistant tuberculosis, treatment with rifampicin, ethambutol, pyrazinamide and levofloxacin is recommended for a duration of 6 months. *(Conditional recommendation, very low certainty in the estimates of effect)*	1.1 In patients with confirmed rifampicin-susceptible, isoniazid-resistant tuberculosis (Hr-TB), treatment with rifampicin, ethambutol, pyrazinamide and levofloxacin is recommended for a duration of 6 months. *(Conditional recommendation, very low certainty in the estimates of effect)* *(No change)*	4.1 In patients with confirmed rifampicin-susceptible, isoniazid-resistant tuberculosis (Hr-TB), treatment with rifampicin, ethambutol, pyrazinamide and levofloxacin is recommended for a duration of 6 months. *(Conditional recommendation, very low certainty of evidence)* *(No change)*
In patients with confirmed rifampicin-susceptible and isoniazid-resistant tuberculosis, it is not recommended to add streptomycin or other injectable agents to the treatment regimen. *(Conditional recommendation, very low certainty in the estimates of effect)*	1.2. In patients with confirmed rifampicin-susceptible, isoniazid-resistant tuberculosis, it is not recommended to add streptomycin or other injectable agents to the treatment regimen. *(Conditional recommendation, very low certainty in the estimates of effect)* *(No change)*	4.2. In patients with confirmed rifampicin-susceptible, isoniazid-resistant tuberculosis, it is not recommended to add streptomycin or other injectable agents to the treatment regimen. *(Conditional recommendation, very low certainty of evidence)* *(No change)*
Section 5: Monitoring patient response to MDR-TB treatment using culture	**Section 5: Monitoring patient response to MDR-TB treatment using culture**	**Section 5: Monitoring patient response to MDR/RR-TB treatment using culture**
In MDR/RR-TB patients on longer regimens, the performance of sputum culture in addition to sputum smear microscopy is recommended to monitor treatment response. It is desirable for sputum culture to be repeated at monthly intervals. *(Strong recommendation, moderate certainty in the estimates of test accuracy)*	5.1. In multidrug- or rifampicin-resistant tuberculosis (MDR/RR-TB) patients on longer regimens, the performance of sputum culture in addition to sputum smear microscopy is recommended to monitor treatment response. *(Strong recommendation, moderate certainty in the estimates of test accuracy)* It is desirable for sputum culture to be repeated at monthly intervals. *(No change)*	5.1. In multidrug- or rifampicin-resistant tuberculosis (MDR/RR-TB) patients on longer regimens, the performance of sputum culture in addition to sputum smear microscopy is recommended to monitor treatment response. *(Strong recommendation, moderate certainty in the estimates of test accuracy)* It is desirable for sputum culture to be repeated at monthly intervals. *(No change)*

Recommendations in the 2019 update	Recommendations in the 2020 update	Recommendations in the 2022 update
Section 6: Start of antiretroviral therapy in patients on second-line antituberculosis regimens	**Section 6: Start of antiretroviral therapy in patients on second-line antituberculosis regimens**	**Section 6: Start of antiretroviral therapy in patients on MDR/RR-TB regimens**
Antiretroviral therapy is recommended for all patients with HIV and DR-TB requiring second-line antituberculosis drugs, irrespective of CD4 cell count, as early as possible (within the first 8 weeks) following initiation of antituberculosis treatment. *(Strong recommendation, very low-quality evidence)*	6.1. Antiretroviral therapy is recommended for all patients with HIV and drug-resistant tuberculosis requiring second-line antituberculosis drugs, irrespective of CD4 cell count, as early as possible (within the first 8 weeks) following initiation of antituberculosis treatment. *(Strong recommendation, very low quality evidence)* *(No change)*	6.1. Antiretroviral therapy is recommended for all patients with HIV and drug-resistant tuberculosis requiring second-line antituberculosis drugs, irrespective of CD4 cell count, as early as possible (within the first 8 weeks) following initiation of antituberculosis treatment. *(Strong recommendation, very low certainty of evidence)* *(No change)*
Section 7: Surgery for patients on MDR-TB treatment	**Section 7: Surgery for patients on MDR-TB treatment**	**Section 7: Surgery for patients on MDR/RR-TB treatment**
In patients with RR-TB or MDR-TB, elective partial lung resection (lobectomy or wedge resection) may be used alongside a recommended MDR-TB regimen. *(Conditional recommendation, very low certainty in the evidence)*	7.1. In patients with rifampicin-resistant tuberculosis (RR-TB) or multidrug-resistant TB (MDR-TB), elective partial lung resection (lobectomy or wedge resection) may be used alongside a recommended MDR-TB regimen. *(Conditional recommendation, very low certainty in the evidence)* *(No change)*	7.1. In patients with rifampicin-resistant tuberculosis (RR-TB) or multidrug-resistant TB (MDR-TB), elective partial lung resection (lobectomy or wedge resection) may be used alongside a recommended MDR-TB regimen. *(Conditional recommendation, very low certainty of evidence)* *(No change)*
Section 8: Care and support for patients with MDR/RR-TB	**Section 8: Care and support for patients with MDR/RR-TB**	**Presented in a separate sub-module of the *WHO consolidated guidelines on tuberculosis. Module 4. Treatment – Tuberculosis care and support (38)***

Annex 2. Trial population in ZeNix and TB-PRACTECAL trials

ZeNix inclusion and exclusion criteria

Inclusion criteria

1. Provide written, informed consent prior to all trial-related procedures (including any additional consent required for participants considered as minors per applicable regulatory authority or ethics committee).
2. Willingness and ability to attend scheduled follow-up visits and undergo study assessments.
3. HIV testing (if an HIV test was performed within 1 month prior to screening, it should not be repeated as long as a documented result can be provided, such as ELISA and/or western blot and/or electro-chemiluminescence). If HIV status is a confirmed known positive, a repeated HIV test is not needed if ELISA and/or western blot and/or electro-chemiluminescence documentation of presence of HIV infection is available.
4. Male or female, aged 14 years and older.

Disease characteristics:

5. Participants with one of the following pulmonary tuberculosis (TB) conditions:
    a. XDR-TB[54] with:
        i. a documented culture positive or a molecular test positive (for *M. tuberculosis*) from a sputum specimen collected within 3 months prior to screening or MTB confirmed in sputum based on molecular test within 3 months prior to or at screening; and
        ii. documented resistance to rifamycins, a fluoroquinolone AND an injectable during the current TB diagnosis/disease course any time prior to or during screening period (may be sensitive or resistant to isoniazid);
    b. Pre-XDR-TB[55] with:
        i. a documented culture positive or a molecular test positive (for MTB) from a sputum specimen collected within 3 months prior to screening or MTB confirmed in sputum based molecular test within 3 months prior to or at screening; and
        ii. documented resistance to rifamycins, and to a fluoroquinolone OR an injectable during the current TB diagnosis/disease course any time prior to or during screening period (may be sensitive or resistant to isoniazid);
    c. MDR-TB with:
        i. a documented culture positive or a molecular test positive (for MTB) from a sputum specimen collected results within 3 months prior to screening or MTB confirmed in sputum based on molecular test within 3 months prior to or at screening; and

[54] In 2021, the definition of XDR-TB changed (see **Definitions**).

[55] In 2021, the definition for pre-XDR-TB changed (see **Definitions**).

ii. documented resistance to rifamycins during the current TB diagnosis/disease course any time prior to or during screening period (may be sensitive or resistant to isoniazid); and

iii. documented non-response to treatment with the best available regimen for 6 months or more prior to enrolment who in the opinion of the investigator have been adherent to treatment and will be adherent to study regimen;

d. MDR-TB with:

i. a documented culture positive or a molecular test positive (for MTB) from a sputum specimen collected within 3 months prior to screening or MTB confirmed in sputum based on molecular test within 3 months prior to or at screening; and

ii. documented resistance to rifamycins during the current TB diagnosis/disease course any time prior to or during screening period (may be sensitive or resistant to isoniazid); and

iii. the inability to continue second-line drug regimen due to a documented intolerance to:

a. PAS, ethionamide, aminoglycosides or fluoroquinolones; or

b. current treatment not listed above that renders the participant eligible for the study in the investigator's opinion.

6. Chest X-ray within 6 months prior to or at screening, obtained and read locally by the investigator or designee with results consistent with pulmonary TB in the opinion of the investigator.

Contraception:

7. Be of non-childbearing potential or using effective methods of birth control, as defined below:

Non-childbearing potential:

a. participant – not heterosexually active or practises sexual abstinence; or

b. female participant or male participant's female sexual partner – bilateral oophorectomy, bilateral tubal ligation and/or hysterectomy or has been postmenopausal with a history of no menses for at least 12 consecutive months;

or

c. male participant or female participant's male sexual partner – vasectomized or has had a bilateral orchidectomy at least 3 months prior to screening.

Effective birth control methods:

a. double barrier method which can include a male condom, diaphragm, cervical cap or female condom; or

b. female participant: barrier method combined with hormone-based contraceptives or an intrauterine device for the female participant; or

c. male participant's female sexual partner: double barrier method or hormone-based contraceptives or an intrauterine device for the female partner;

and are willing to continue practising birth control methods throughout treatment and for 6 months (female participants) and 12 weeks (male participants) after the last dose of study medication.

Exclusion criteria

Medical history and concurrent conditions:

1. Any condition in the investigator's opinion (e.g. an unstable disease such as uncontrolled diabetes or cardiomyopathy, extrapulmonary TB requiring extended treatment, cancer that could affect survival through the protocol-specified follow-up period), where participation in the trial would compromise the well-being of the participant or prevent, limit or confound protocol-specified assessments.

2. Abuse of alcohol or illegal drugs that in the opinion of the investigator would compromise a participant's safety or ability to follow through with all protocol-specified restrictions, visits and evaluations.
3. In the judgement of the investigator, the participant is not expected to survive for more than 6 months.
4. Karnofsky score <60 at screening.
5. History of allergy or known hypersensitivity to any of the trial investigational medicinal products or related substances.
6. Body mass index (BMI) <17 kg/m^2.
7. TB infection with historic drug susceptibility testing (DST) or the minimum inhibitory concentration (MIC) results with values suggesting likely resistance to pretomanid, delamanid, linezolid or bedaquiline; the Sponsor Medical Monitor must be consulted to help interpret any available historic results.
8. Participants who, upon the evaluation of their pulmonary disease, are expected to require a surgical procedure.
9. Having participated in other clinical studies with dosing of investigational agents within 8 weeks prior to screening or currently enrolled in an investigational study that includes treatment with medicinal agents. Participants who are participating in observational studies or who are in a follow-up period of a trial that included drug therapy may be considered for inclusion.
10. Participants with any of the following at screening:
    a. corrected QT interval by Fredericia (QTcF) interval on electrocardiogram (ECG) >500 msec. Participants with QTcF >450 must be discussed with and approved by the Sponsor Medical Monitor before enrolment (per measurements and reading done from screening central ECG);
    b. heart failure;
    c. a personal or family history of congenital QT prolongation;
    d. a history of or known, untreated, ongoing hypothyroidism;
    e. a history of or ongoing bradyarrhythmia; or
    f. a history of torsades de pointes.
11. Females who have a positive pregnancy test at screening or are already known to be pregnant, breastfeeding or planning to conceive a child during the study or within 6 months of cessation of treatment; and males planning to conceive a child during the study or within 6 months of cessation of treatment.
12. A peripheral neuropathy of Grade 3 or 4, according to DMID . Or participants with a Grade 1 or 2 neuropathy which is likely to progress or worsen over the course of the study, in the opinion of the investigator.

Previous and concomitant therapy

13. Known (during screening) requirement for future concomitant (during treatment) use of any prohibited and/or avoided medications noted in Section 5.3 (of the trial protocol).
14. Prior use of monoamine oxidase inhibitors (MAOIs) within 2 weeks of randomization.
15. Prior use of serotonergic antidepressants within 3 days of randomization if the investigator foresees potential risks for serotonin syndrome when combined with linezolid.
16. Participants who have received more than 2 weeks of bedaquiline, linezolid or delamanid prior to the first dose of IMP.
17. Participants with newly diagnosed TB and HIV that require initiation of appropriate HIV therapy before the participant has received at least 2 weeks of an antituberculosis regimen.

18. HIV infected participants with planned continued use of zidovudine, stavudine or didanosine. The antiretroviral therapy (ART) booster cobicistat should not be used. Please reference restrictions Section 5.3.3 (of the trial protocol) Antiretroviral Therapy, for guidance on ART treatment during the treatment period.

Diagnostic and laboratory abnormalities

19. Participants with any of the following toxicities at screening (laboratories may be repeated during the screening period) as defined by the enhanced (DMID) adult toxicity table (November 2007):
    a. viral load >1 000 copies/mL (unless newly diagnosed HIV and not yet on ART and who otherwise qualify for participation);
    b. CD4+ count <100 cells/µL (HIV positive participants);
    c. serum potassium less than the lower limit of normal for the laboratory;
    d. haemoglobin <9.0 g/dL or <90 g/L;
    e. platelets <100 000/mm^3 or <100 × 10^9/L;
    f. absolute neutrophil count (ANC) <1 500/mm^3 or <1.5 × 10^9/L;
    g. aspartate aminotransferase (AST):
        – Grade 3 or greater (>3.0 × ULN) to be excluded;
        – results between 1.5 × ULN and 3 × ULN must be discussed with and approved by the Sponsor Medical Monitor;
    h. alanine aminotransferase:
        – Grade 3 or greater (>3.0 × ULN) to be excluded;
        – results between 1.5 × ULN and 3 × ULN must be discussed with and approved by the Sponsor Medical Monitor;
    i. total bilirubin:
        – greater than 1.5 × ULN to be excluded;
        – 1–1.5 × ULN must be discussed with and approved by the Sponsor Medical Monitor;
    j. direct bilirubin:
        – greater than ULN to be excluded;
    k. serum creatinine level greater than 1.5 times upper limit of normal; and
    l. albumin <3.0 g/dl or <30 g/L.

TB-PRACTECAL inclusion and exclusion criteria

Inclusion criteria

- Male or female patients aged 15 years or above (where locally approved), regardless of HIV status.
- Microbiological test (molecular or phenotypic) confirming the presence of *M. tuberculosis* in sputum.
- Resistant to at least rifampicin by either molecular or phenotypic drug susceptibility test.
- Completed informed consent form (ICF).

Exclusion criteria

- Known allergies, hypersensitivity or intolerance to any of the study drugs.
- Pregnant, breastfeeding or unwilling to use appropriate contraceptive measures if of childbearing potential.

- Alanine transaminase (ALT) and/or aspartate transaminase (AST) and/or bilirubin >3 times the upper limit of normal.
- Taking any medications contraindicated with the medicines in the trial.
- QTcF >450 ms.
- One or more risk factors for QTc prolongation (excluding age and gender) or other uncorrected risk factors for torsades de pointes.
- History of cardiac disease, syncopal episodes, symptomatic or significant asymptomatic arrhythmias (with the exception of sinus arrhythmia).
- Any baseline laboratory value consistent with Grade 4 toxicity.
- Moribund.
- Known resistance to bedaquiline, pretomanid, linezolid or delamanid.
- Any other condition (social or medical) which, in the opinion of the investigator, would make study participation unsafe.
- Prior use of bedaquiline and/or pretomanid and/or linezolid and/or delamanid for 1 or more months.
- Patients not eligible to start a new course of MDR-TB or XDR-TB[56] treatment according to local protocol, for reasons including but not limited to:
  a. currently on MDR-TB treatment for at least 2 weeks (and not failing);
  b. no permanent physical address;
  c. loss to follow-up in previous treatment with no change in circumstance and motivation.
- Tuberculous meningoencephalitis, brain abscesses, osteomyelitis or arthritis.

[56] In 2021, the definition for pre-XDR-TB changed (see **Definitions**).

For further information, please contact:

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